07/841,617

07/841/617

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 5,310,912

Issue Date: May 10, 1994

Patentees: John L. Neumeyer, Richard A. Milius and Robert B. Innis

For: IODINATED NEUROPROBE FOR MAPPING MONOAMINE REUPTAKE SITES

Commissioner for Patents
Mail Stop Patent Extension
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION FOR EXTENSION OF PATENT TERM FOR U.S. PATENT NO. 5,310,912 UNDER 35 U.S.C. § 156 FOR DATSCAN (IOFLUPANE I 123 INJECTION) FOR INTRAVENOUS USE

Dear Sir:

GE Healthcare Limited ("Applicant") hereby requests an extension of the term of U.S. Patent No. 5,310,912 under 35 U.S.C. § 156. Applicant is the owner of the entire right, title and interest in U.S. Patent No. 5,310,912 by virtue of assignments recorded in the U.S. Patent and Trademark Office on the following dates:

May 20, 1992, at Reel 006125, Frame 0580
May 20, 1992, at Reel 006125, Frame 0576
December 5, 1992, at Reel 006325, Frame 0639
December 3, 1992, at Reel 006408, Frame 0127
May 19, 1997, at Reel 008503, Frame 0562
March 30, 1998, at Reel 009064, Frame 0309
June 24, 2002, at Reel 013019, Frame 0531
July 29, 2002, at Reel 013117, Frame 0806
October, 18, 2005, at Reel 016891, Frame 0728
November 30, 2005, at Reel 017073, Frame 0846

04/12/2011 RLOGAN 00000001 502665 07841617
01 FC:1457 1120.00 DA

Copies of the Patent Assignment Abstract of Title and Statement Under 37 C.F.R. § 3.73(b) are attached hereto as Exhibit "A".

Applicant submits the following information under 35 U.S.C. § 156 and 37 C.F.R. § 1.740. For convenience, the requirements of 37 C.F.R. § 1.740(a) are, in relevant part, set forth below in bold according to the numerical format set forth therein, and the information submitted in accordance with the requirements is set forth thereunder.

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.

The approved product is DaTscan (Ioflupane I 123 Injection) for Intravenous Use ("DaTscan"). The active ingredient in DaTscan is [^{123}I]ioflupane. DaTscan is further identified as follows:

Chemical Name. DaTscan is the trade name of a formulation which contains the (radio)active drug substance [^{123}I]ioflupane. The non-radioactive chemical compound, ioflupane, is present in about 25-fold excess over the radioactive molecules. The International Union of Pure and Applied Chemistry ("IUPAC") chemical name for the radioactive drug substance is: Methyl (1*R*-2*S*-3*S*-5*S*)-8-(3-fluoropropyl)-3-(4-[^{123}I]iodophenyl)-8-azabicyclo[3.2.1] octane-2-carboxylate.

Alternative Chemical Names. Alternative chemical names for [^{123}I]ioflupane include:

N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-[^{123}I]iodophenyl)nortropane;
^{123}I-FP-CIT,
^{123}I-CIT-FP,
^{123}I-β-FP-CIT,
^{123}I-β-CIT-FP;
^{123}I-RTI-313.
Chemical Abstracts index names: 8-Azabicyclo[3.2.1]octane-2-carboxylic acid, 8-(3-fluoropropyl)-3-[4-(iodo-^{123}I)phenyl]-, methyl ester, (1R,2S,3S,5S).
The Chemical Abstracts Registry Number: 155798-07-5.
8-Azabicyclo[3.2.1]octane-2-carboxylic acid, 8-(3-fluoropropyl)-3-[4-(iodo-^{123}I)phenyl]-methyl ester, [1R,-(exo, exo)]-.

Alternative chemical names for non-radioactive ioflupane include:

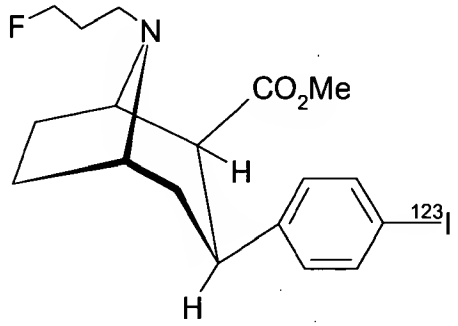
N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane;
FP-CIT,
CIT-FP,
β-FP-CIT,
β-CIT-FP;
RTI-313.
Chemical Abstracts index names:
8-Azabicyclo[3.2.1]octane-2-carboxylic acid, 8-(3-fluoropropyl)-3-(4-iodophenyl)-methyl ester, (1R,2S,3S,5S).
Chemical Abstracts Registry Number: 155797-99-2.

8-Azabicyclo[3.2.1]octane-2-carboxylic acid, 8-(3-fluoropropyl)-3-(4-iodophenyl)-methyl ester, [1R,-(exo, exo)]-.

Generic name. The generic name of DaTscan is [^{123}I]ioflupane or Ioflupane (^{123}I).

Molecular Formula and Weight. The molecular formula of DaTscan is $C_{18}H_{23}F[^{123}I]NO_2$. The relative molecular mass is 431.29 (for the non-radioactive ioflupane molecule).

Physical Structure. The chemical formula of [^{123}I]ioflupane is:



Physical Description and Characteristics. DaTscan is a sterile, pyrogen-free radiopharmaceutical for intravenous injection. The clear and colorless solution is supplied in single-use vials in which each milliliter contains 0.07 to 0.13 µg ioflupane, 74 MBq (2 mCi) of iodine 123 (as ioflupane I 123) at calibration time, 5.7 mg acetic acid, 7.8 mg sodium acetate and 0.05 mL (5%) ethanol. The pH of the solution is between 4.2 and 5.2. Ioflupane I 123 is a cyclotron-produced radionuclide that decays to ^{123}Te by electron capture and has a physical half-life of 13.2 hours.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.

DaTscan was subject to regulatory review under section 505(b) of the Federal Food, Drug, and Cosmetic Act ("FD&C Act"), which is codified at 21 U.S.C. § 355(b).

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.

DaTscan was approved for commercial marketing or use on January 14, 2011, under FD&C Act § 505(b). Specifically, DaTscan was approved for striatal dopamine transporter visualization using single photon emission computed tomography brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian Syndromes.

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act . . . .

DaTscan is a drug product, and the active ingredient in DaTscan is [^{123}I]ioflupane. [^{123}I]ioflupane has not previously been approved for commercial marketing or use under either the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the date of the last day on which the application could be submitted.

This application is being submitted within the 60-day period permitted for its submission under 37 C.F.R. § 1.720(f). The last day on which this application could be submitted is March 14, 2011.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.

The patent for which an extension is being sought is identified as follows:

Inventors. John L. Neumeyer, Richard A. Milius and Robert B. Innis

Patent Number. 5,310,912

Date of Issue. May 10, 1994

Date of Expiration. February 25, 2012.

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.

A copy of Patent No. 5,310,912, the patent for which an extension is being sought, is attached hereto as Exhibit "B".

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.

Applicant is not aware of any disclaimer or reexamination certificate being issued for Patent No. 5,310,912. A Certificate of Correction was requested and issued and is attached hereto as Exhibit "C". Maintenance fees have been paid, per the attached Exhibit "D".

(9) A statement that the patent claims the approved product . . . and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on . . . [t]he approved product, if the listed claims include any claim to the approved product . . . .

Claims 1 and 2 of Patent No. 5,310,912 claim the approved product, DaTscan, as follows:

Claim 1. DaTscan is an iodinated neuroprobe for mapping monoamine reuptake sites. In the formula of Claim 1, DaTscan has:

R = 3-fluoropropyl which is a monofluoroalkyl group including ^{n}F, where $^{n}F = {}^{19}F$ i.e. n is 19;
R′ = CH_3 i.e. a C_nH_{2n+1} group where n = 0-6 where n = 1;
Y = H;
X = an isotope of I (iodine).

Therefore, Claim 1 reads on the approved product.

Claim 2. X = ^{123}I. Therefore, Claim 2 reads on the approved product.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services . . . to determine the applicable regulatory review period . . . .

The relevant dates of the testing phase and the approval phase for DaTscan that will enable the Secretary of Health and Human Services to determine the applicable regulatory review period under 35 U.S.C. § 156(g) are as follows:

Testing Phase. The approval of DaTscan by the U.S. Food and Drug Administration ("FDA") was based on two clinical studies: Study 003 and Study 304, both of which were conducted outside the United States. *See* FDA, Center for Drug Evaluation and Research, *Summary Review for Regulatory Action*, Jan. 5, 2011, at 7-8 (stating that the "safety and efficacy of DaTscan were evaluated in two multicenter, single-arm studies (Study 304 and Study 003) that evaluated 287 adult patients with tremor").[1] When the clinical trials for a product are conducted outside the United States, and there is not an investigational new drug ("IND") application or IND number, the testing phase begins on the date the clinical investigation was begun. *Cf.* U.S. Patent and Trademark Office ("PTO"), Final Rule, *Rules for Extension of Patent Term*, 52 Fed. Reg. 9,386, 9,388 (Mar. 24, 1987) (stating that "when the clinical trials are conducted outside the United States, the testing phase for a medical device begins on the date the clinical investigation involving the device was begun"). The clinical trials for DaTscan were conducted as follows:

- *Study 003.* A Clinical Trial Exemption ("CTX") in the United Kingdom became effective for DaTscan on June 19, 1997. For purposes of determining the applicable regulatory review period, a CTX is equivalent to an IND exemption under FD&C Act § 505(i).[2] The CTX (#00221/0134/A) permitted a Phase III clinical study (#DP008-003) on DaTscan that commenced on August 25, 1997, and was completed on February 24, 1998.[3]

- *Study 304.* The CTX (#00221/0134/A) was broadened on December 14, 1998 (and later was converted to an approved clinical trial application ("CTA")).[4] The CTX/CTA

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[1] A copy of the Summary Review is attached hereto as Exhibit "E".

[2] A copy of the CTX (#00221/0134/A) is attached hereto as Exhibit "F".

[3] A copy of the Study 003 report is attached hereto as Exhibit "G". The clinical investigation for DaTscan actually commenced sometime prior to April 25, 1996, when the Applicant obtained Ethics Committee ("EC") approval to conduct a Phase I clinical study of DaTscan in the Netherlands. The Applicant has been unable to obtain documentation of the EC approval and therefore does not assert herein that the testing phase of the regulatory review period commenced earlier than June 19, 1997.

[4] A copy of the correspondence broadening CTX (#00221/0134/A) and converting it to an approved CTA (#00221/0134/001) is attached hereto as Exhibit "H".

permitted another Phase III clinical study (#PDT304) on DaTscan. Study 304 commenced on January 18, 1999, and was completed on June 28, 2005.[5]

Approval Phase. The approval phase is as follows:

- *March 6, 2009.* Applicant initially submitted a New Drug Application ("NDA") for DaTscan to the FDA on March 6, 2009, under FD&C Act § 505(b), as NDA No. 22-454.[6]

- *January 14, 2011.* The FDA approved NDA No. 22-454 on January 14, 2011.[7]

[5] A copy of the Study 304 report is attached hereto as Exhibit "I".

[6] A copy of the complete response letter that Applicant received from the FDA, which references the date Applicant initially submitted the NDA, is attached hereto as Exhibit "J".

[7] A copy of the NDA approval letter is attached hereto as Exhibit "K".

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

A brief description of the activities undertaken by Applicant during the applicable regulatory review period with respect to DaTscan is set forth below as a chronology of some of the significant events from April 25, 1996, to January 14, 2011:

1. Prior to April 25, 1996 -- Applicant obtains Ethics Committee ("EC") approval for Phase I study of DaTscan in the Netherlands.

2. April 25, 1996 to June 27, 1996 -- Phase I study of DaTscan is conducted in the Netherlands.

3. December 10, 1996 -- Applicant obtains EC approval for Phase II study of DaTscan in the Netherlands.

4. January 7, 1997 to March 21, 1997 -- Phase II study of DaTscan is conducted in the Netherlands.[8]

5. June 19, 1997 -- Applicant obtains a CTX (#00221/0134/A) for DaTscan in the United Kingdom.

6. August 25, 1997 -- Study 003 of DaTscan is conducted under CTX #00221/0134/A.

7. February 24, 1998 -- Study 003 is completed.

8. November 24, 1998 -- Applicant submits application for marketing approval for DaTscan in Europe.

9. December 4, 1998 -- CTX #00221/0134/A is broadened to permit Study 304.

10. January 18, 1999 -- Study 304 of DaTscan is conducted under broadened CTX #00221/0134/A (which later is converted to CTA #00221/0134/001).

11. June 28, 2005 -- Study 304 is completed.

12. July 27, 2000 -- DaTscan is approved for marketing in Europe.[9]

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[8] Applicant has been unable to locate original documentation of the EC approvals for the Phase I and Phase II studies of DaTscan. The study report for the Phase II study, which documents EC approval for that study, was located and relevant pages are attached hereto as Exhibit "L".

[9] A copy of the European Commission marketing authorization for DaTscan is attached hereto as Exhibit "M".

13. March 6, 2009 -- Applicant submits an NDA for DaTscan to the FDA.

14. January 14, 2011 -- FDA approves NDA for DaTscan.

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined.

Applicant is of the opinion that Patent No. 5,310,912 is eligible for an extension under 35 U.S.C. § 156. The length of the extension claimed is five years.

First, the eligibility requirements of 35 U.S.C. §§ 156(a) and 156(c)(4) have been satisfied as follows:

- Patent No. 5,310,912 claims a product, DaTscan.
- Patent No. 5,310,912 is currently set to expire on February 25, 2012 (i.e., the term of the patent has not yet expired).
- The term of Patent No. 5,310,912 has never been extended under 35 U.S.C. § 156(e)(1).
- This application for extension is being submitted by Applicant, the owner of record of Patent No. 5,310,912, in accordance with 35 U.S.C. § 156(d)(1)-(4).
- The product, DaTscan, has been subject to a regulatory review period under FD&C Act § 505(b) before its commercial marketing or use in the United States, and the permission for DaTscan's commercial marketing or use in the United States is the first permitted commercial marketing or use of the product under FD&C Act § 505(b).
- To this date, no patent has been extended, nor has any other extension been applied for, under 35 U.S.C. § 156(e)(1), for the regulatory review period which forms the basis for this application for extension of the term of Patent No. 5,310,912.
- Applicant has submitted this application within 60 days of the date that Applicant received permission from FDA for the commercial marketing or use of DaTscan.

Second, the length of extension of the term of Patent No. 5,310,912 of five years that is claimed by Applicant was determined according to the provisions of 37 C.F.R. § 1.775 as follows:

- According to 37 C.F.R. § 1.775(b), the patent term will be extended by the length of the regulatory review period for the approved product, reduced as appropriate pursuant to 37 C.F.R. § 1.775(d)(1)-(6).
- According to 37 C.F.R. §1.775(c), the regulatory review period is the sum of:
    - The number of days in the period beginning on the date the IND (or CTX equivalent) became effective and ending on the date the NDA was initially submitted (i.e., the testing phase); and

- The number of days in the period beginning on the date the NDA was initially submitted and ending on the date the NDA was approved (i.e., the approval phase).

- Here, the CTX for DaTscan (the IND equivalent) became effective on June 19, 1997, and the NDA for DaTscan was initially submitted on March 6, 2009. Hence, the testing phase for DaTscan under 37 C.F.R. § 1.775(c)(1) is 4,278 days. The NDA for DaTscan was initially submitted on March 6, 2009, and the NDA was approved on January 14, 2011. Hence, the approval phase for DaTscan under 37 C.F.R. § 1.775(c)(2) is 679 days.

- The regulatory review period under 37 C.F.R. §1.775(c) is the sum of the testing phase (4,278 days) and the approval phase (679 days), which is 4,957 days.

- According to 37 C.F.R. §1.775(d)(l)(i), the number of days in the regulatory review period that were on and before the date on which the patent issued must be subtracted. Here, Patent No. 5,310,912 issued on May 10, 1994; the testing phase did not commence until June 19, 1997. Thus, no days in the regulatory review period occurred before the patent issued and therefore no days must be subtracted from the regulatory review period.

- 37 C.F.R. § 1.775(d)(l)(ii) does not apply because Applicant acted with due diligence during the regulatory review period.[10]

- According to 37 C.F.R. § 1.775(d)(l)(iii), one-half of the number of days of the testing phase must be subtracted. Here, this is one-half of 4,278 days, which is 2,139 days. After subtraction, this leaves a reduced regulatory review period of 2,139 days plus 679 days, which is 2,818 days.

- According to 37 C.F.R. § 1.775(d)(2), the reduced regulatory review period of 2,818 days must be added to the expiration date of Patent No. 5,310,912 (i.e., February 25, 2012). This gives a date of November 19, 2019. According to 37 C.F.R. § 1.775(d)(3), 14 years must be added to the date of approval of the approved product. This gives a date of January 14, 2025. According to 37 C.F.R. § 1.775(d)(4), the earlier of these dates must

[10] It may be argued that the testing phase ended on June 28, 2005, when Study 304 (one of the two studies FDA relied on in approving the DaTscan NDA) was completed. The approval phase did not begin until March 6, 2009, when Applicant initially submitted the DaTscan NDA to FDA. Even if FDA were to determine that Applicant did not act with due diligence during this 1,347-day period during the regulatory review period, *see* 21 C.F.R. § 60.36(a), such 1,347-day period would not affect the maximum patent extension the Applicant is seeking in this application, *see* 37 C.F.R. § 1.775(d). As such, FDA should deny any due diligence petition alleging as much. *See* 21 C.F.R. § 60.34(b)(5) (stating that FDA should deny a due diligence petition that "fails to allege a sufficient total amount of time during which the applicant did not exercise due diligence such that, even if the petition were granted, the petition would not affect the maximum patent extension the applicant sought in the application").

be selected. The earlier of these dates is November 19, 2019, which is 2,824 days beyond the expiration date of the 5,310,912 patent.

- The provisions of 37 C.F.R. § 1.775(d)(5) apply to this application because Patent No. 5,310,912 issued after September 24, 1984. Pursuant to 37 C.F.R. § 1.775(d)(5)(i), five years are added to the expiration date of Patent No. 5,310,912 (i.e., February 25, 2012) giving a date of February 25, 2017. According to 37 C.F.R. § 1.775(d)(5)(ii), the dates obtained pursuant to 37 C.F.R. § 1.775(d)(5)(i) and 37 C.F.R. § 1.775(d)(4) are compared and the earlier date is selected. The date calculated according to 37 C.F.R. § 1.775(d)(4) above is November 19, 2019, and the date calculated according to 37 C.F.R. § 1.775(d)(5)(i) is February 25, 2017. Therefore, the earlier of these dates is February 25, 2017. Applicant is entitled to an extension of the term of Patent No. 5,310,912 until February 25, 2017, i.e., an extension of five years from the original expiration date of February 25, 2012.

- 37 C.F.R. § 1.775(d)(6) does not apply because Patent No. 5,310,912 issued on May 10, 1994, which was after September 24,1984.

(13) A statement that applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought (*see* § 1.765).

Applicant acknowledges a duty to disclose to the Director of the U.S. Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension of five years which is being sought to the term of Patent No. 5,310,912.

(14) The prescribed fee for receiving and acting upon the application for extension (see § 1.20(j)).

The prescribed fee under 37 C.F.R. § 1.20(j) for receiving and acting on this application for patent term extension is $1,120.00. Please charge the sum of $1,120.00 to Deposit Account No. 502665. In addition, please charge any underpayment or any additional fees that may be required, or credit any overpayment, to Deposit Account No. 502665.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.

Please direct all inquiries and correspondence relating to this application for patent term extension as follows:

Christine S. Lee, Ph.D., J.D.
Intellectual Property Counsel
GE Healthcare
101 Carnegie Center
Princeton, New Jersey 08540
(609) 514-6418 telephone
(609) 514-6572 facsimile
Christine.Lee@ge.com

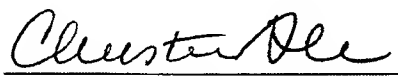
* * *

Pursuant to 37 C.F.R. § 1.740(b), two additional copies of this application are enclosed herewith.

Applicant respectfully requests prompt and favorable action on the merits of this application for extension of the term of Patent No. 5,310,912 of five years, based on the regulatory review period for DaTscan.

Sincerely,

GE HEALTHCARE



Christine S. Lee
Attorney for Applicant
Reg. No. 42,788
(609) 514-6418 telephone
(609) 514-6572 facsimile

United States Patent and Trademark Office

Assignments on the Web > Patent Query

Patent Assignment Abstract of Title

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Total Assignments: 10

Patent #: 5310912 **Issue Dt:** 05/10/1994 **Application #:** 07841617 **Filing Dt:** 02/25/1992

Inventors: JOHN L. NEUMEYER, RICHARD A. MILIUS, ROBERT B. INNIS

Title: IODINATED NEUROPROBE FOR MAPPING MONOAMINE REUPTAKE SITES

Assignment: 1

Reel/Frame: 006125/0580 **Recorded:** 05/20/1992 **Pages:** 3

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST.

Assignor: INNIS, ROBERT B. **Exec Dt:** 03/12/1992

Assignee: RESEARCH BIOCHEMICALS INCORPORATED
ONE STRATHMORE ROAD
A MA CORPORATION
NATICK, MASSACHUSETTS 01760

Correspondent: STANLEY M. SCHURGIN
WEINGARTEN, SCHURGIN, GAGNEBIN & HAYES
TEN POST OFFICE SQUARE
BOSTON, MA 02109

Assignment: 2

Reel/Frame: 006125/0576 **Recorded:** 05/20/1992 **Pages:** 4

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST.

Assignors: NEUMEYER, JOHN L. **Exec Dt:** 04/21/1992
MILIUS, RICHARD A. **Exec Dt:** 04/20/1992

Assignee: RESEARCH BIOCHEMICALS INCORPORATED A MA CORPORATION
ONE STRATHMORE ROAD
NATICK, MASSACHUSETTS 01760

Correspondent: STANLEY M. SCHURGIN
WEINGARTEN, SCHURGIN, GAGNEBIN & HAYES
TEN POST OFFICE SQUARE
BOSTON, MA 02109

Assignment: 3

Reel/Frame: 006325/0639 **Recorded:** 12/05/1992 **Pages:** 2

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST.

Assignor: RESEARCH BIOCHEMICALS INCORPORATED **Exec Dt:** 11/25/1992

Assignee: RESEARCH BIOCHEMICALS LIMITED PARTNERSHIP
ONE STRATHMORE ROAD
NATICK, MASSACHUSETTS 01760

Correspondent: PAUL C. DESJOURDY, ESQ.
CHOATE, HALL & STEWART
EXCHANGE PLACE
53 STATE STREET
BOSTON, MA 02109

Assignment: 4

Reel/Frame: 006408/0127 **Recorded:** 12/03/1992 **Pages:** 3

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST.

Assignor: RESEARCH BIOCHEMICALS INCORPORATED **Exec Dt:** 11/25/1992

Assignee: RESEARCH BIOCHEMICALS LIMITED PARTNERSHIP
ONE STRATHMORE ROAD
NATICK, MASSACHUSETTS 01760

Correspondent: WEINGARTEN, SCHURGIN, GAGNEBIN & HAYES
STANLEY M. SCHURGIN ESQ.
TEN POST OFFICE SQUARE
BOSTON, MA 02109

Assignment: 5

Reel/Frame: 008503/0562 **Recorded:** 05/19/1997 **Pages:** 5

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignor: RESEARCH BIOCHEMICALS, LIMITED PARTNERSHIP (DBA RESEARCH BIOCHEMICALS INTERNATIONAL) **Exec Dt:** 05/13/1997

Assignee: NEURO IMAGING TECHNOLOGIES, LLC
1 EXETER PLAZA
BOSTON, MASSACHUSETTS 02116

Correspondent: WEINGARTEN, SCHURGIN, GAGNEBIN & HAYES
STANLEY M. SCHURGIN
TEN POST OFFICE SQUARE
BOSTON, MA 02109

Assignment: 6

Reel/Frame: 009064/0309 **Recorded:** 03/30/1998 **Pages:** 6

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignor: NEURO IMAGING TECHNOLOGIES, LLC **Exec Dt:** 03/19/1998

Assignee: NYCOMED AMERSHAM PLC
466 DEVON PARK DRIVE
WAYNE, PENNSYLVANIA 19087

Correspondent: WEINGARTEN, SCHURGIN, GAGNEBIN ET AL.
STANLEY M. SCHURGIN
TEN POST OFFICE SQUARE
BOSTON, MA 02109

Assignment: 7

Reel/Frame: 013019/0531 **Recorded:** 06/24/2002 **Pages:** 4

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignor: NEURO IMAGING TECHNOLOGIES, LLC **Exec Dt:** 03/19/1998

Assignee: NYCOMED AMERSHAM PLC
466 DEVON PARK DRIVE
WAYNE, PENNSYLVANIA 19087

Correspondent: WEINGARTEN SCHURGIN GAGNEBIN & LEBOVICI
HOLLIDYA C. HEINE
TEN POST OFFICE SQUARE
BOSTON, MA 02109

Assignment: 8

Reel/Frame: 013117/0806 **Recorded:** 07/29/2002 **Pages:** 3

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignor: NYCOMED AMERSHAM PLC **Exec Dt:** 07/12/2001

Assignee: AMERSHAM PLC
THE GROVE CENTRE, WHITE LION ROAD
AMERSHAM, BUCKINHAMSHIRE, GREAT BRITAIN HP7 9

Correspondent: WEINGARTEN, SCHURGIN, GAGNEBIN, ET AL.
HOLLIDAY C. HEINE
TEN POST OFFICE SQUARE
BOSTON, MA 02109

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Conveyance: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).

Assignor: AMERSHAM PLC **Exec Dt:** 08/25/2005

Assignee: GE HEALTHCARE LIMITED
AMERSHAM PLACE
LITTLE CHALFONT
BUCKINGHAMSHIRE HP7 9NA, UNITED KINGDOM

Correspondent: AMERSHAM HEALTH, INC.
ROBERT F. SHISHOLM
101 CARNEGLE CENER
IP DEPARTMENT
PRINCETON, NJ 08540

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Conveyance: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).

Assignor: AMERSHAM PLC **Exec Dt:** 08/25/2005

Assignee: GE HEALTHCARE LIMITED
LITTLE CHALFONT
AMERSHAM PLACE, LITTLE CHALFONT
BUCKINGHAMSHIRE, HP7 9NA, UNITED KINGDOM

Correspondent: ROBERT F. CHISHOLM
AMERSHAM HEALTH, INC.
IP DEPARTMENT
101 CARNEGIE CENTER
PRINCETON, NJ 08540

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: GE HEALTHCARE LIMITED

Application No./Patent No.: 5310912 Filed/Issue Date: MAY 10, 1994

Titled: IODINATED NEUROPROBE FOR MAPPING MONOAMINE REUPTAKE SITES

GE HEALTHCARE LIMITED , a CORPORATION

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy therefore is attached.

OR

B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

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2. From: JOHN L. NEUMEYER To: RESEARCH BIOCHEMICALS INCORPORATED

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☒ Additional documents in the chain of title are listed on a supplemental sheet(s).

☐ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature — 6th MARCH 2011 Date

Michael Murphy Printed or Typed Name — Director Title

Patent Number 5,310,912 Issue Date: May 10, 1994

CONTINUATION PAGE OF THE CHAIN OF TITLE OF FORM 3.73(b)

From: Research Biochemicals Incorporated **To**: Research Biochemicals Limited Partnership
December 5, 1992, at Reel 006325, Frame 0639

From: Research Biochemicals Incorporated **To**: Research Biochemicals Limited Partnership
December 3, 1992, at Reel 006408, Frame 0127

From: Research Biochemicals Limited Partnership **To**: Neuro Imaging Technologies, LLC
May 19, 1997, at Reel 008503, Frame 0562

From: Neuro Imaging Technologies, LLC **To**: Nycomed Amersham PLC
March 30, 1998, at Reel 009064, Frame 0309

From: Neuro Imaging Technologies, LLC **To**: Nycomed Amersham PLC
June 24, 2002, at Reel 013019, Frame 0531

From: Nycomed Amersham PLC **To**: Amersham PLC
July 29, 2002 at Reel 013117, Frame 0806

From: Amersham PLC **To**: GE Healthcare Limited
October, 18, 2005, at Reel 016891, Frame 0728

From: Amersham PLC **To**: GE Healthcare Limited
November 30, 2005, at Reel 017073, Frame 0846

Exhibit B

US005310912A

United States Patent [19]

Neumeyer et al.

[11] Patent Number: 5,310,912

[45] Date of Patent: May 10, 1994

[54] IODINATED NEUROPROBE FOR MAPPING MONOAMINE REUPTAKE SITES

[75] Inventors: John L. Neumeyer, Wayland; Richard A. Milius, Boston, both of Mass.; Robert B. Innis, Hamden, Conn.

[73] Assignee: Research Biochemicals Limited Partnership, Natick, Mass.

[21] Appl. No.: 841,617

[22] Filed: Feb. 25, 1992

[51] Int. Cl.[5] C07D 451/02

[52] U.S. Cl. 546/132

[58] Field of Search 424/1.1; 546/125, 132, 546/124; 514/304

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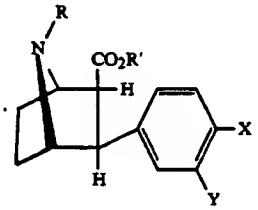
(List continued on next page.)

Primary Examiner—Robert L. Stoll
Assistant Examiner—Lara E. Chapman
Attorney, Agent, or Firm—Weingarten, Schurgin, Gagnebin & Hayes

[57] ABSTRACT

An iodinated neuroprobe is provided for mapping monoamine reuptake sites. The iodinated neuroprobe is of the formula:



wherein

R=a C_nH_{2n+1} group where n=0–6, an alkenyl group, a monofluoroalkyl group including ^{n}F where n=18 or 19, or a $^{m}C_nH_{2n+1}$ group where n=1–6 and where m=11 or 14 for at least one ^{m}C;

R'=a C_nH_{2n+1} group where n=0–6, a p-iodophenylmethyl group, a p-iodophenylethyl group, a phenylmethyl group, or a phenylethyl group;

X=an isotope of F, an isotope of Cl, an isotope of Br, an isotope of I, CH_3, or $Sn(R''_1R''_2R''_3)$;

R''_1=a C_nH_{2n+1} group where n=1–6, or an aryl group;

R''_2=a C_nH_{2n+1} group where n=1–6, or an aryl group;

R''_3=a C_nH_{2n+1} group where n=1–6, or an aryl group; and

Y=H only if X is an isotope of I, or R' is a p-iodophenylmethyl group, or R' is a p-iodophenylethyl group, else Y=an isotope of I.

Related analogs are also provided. Additionally, a precursor of a radiolabled neuroprobe and a kit for preparing the iodinated neuroprobe are provided.

8 Claims, 4 Drawing Sheets

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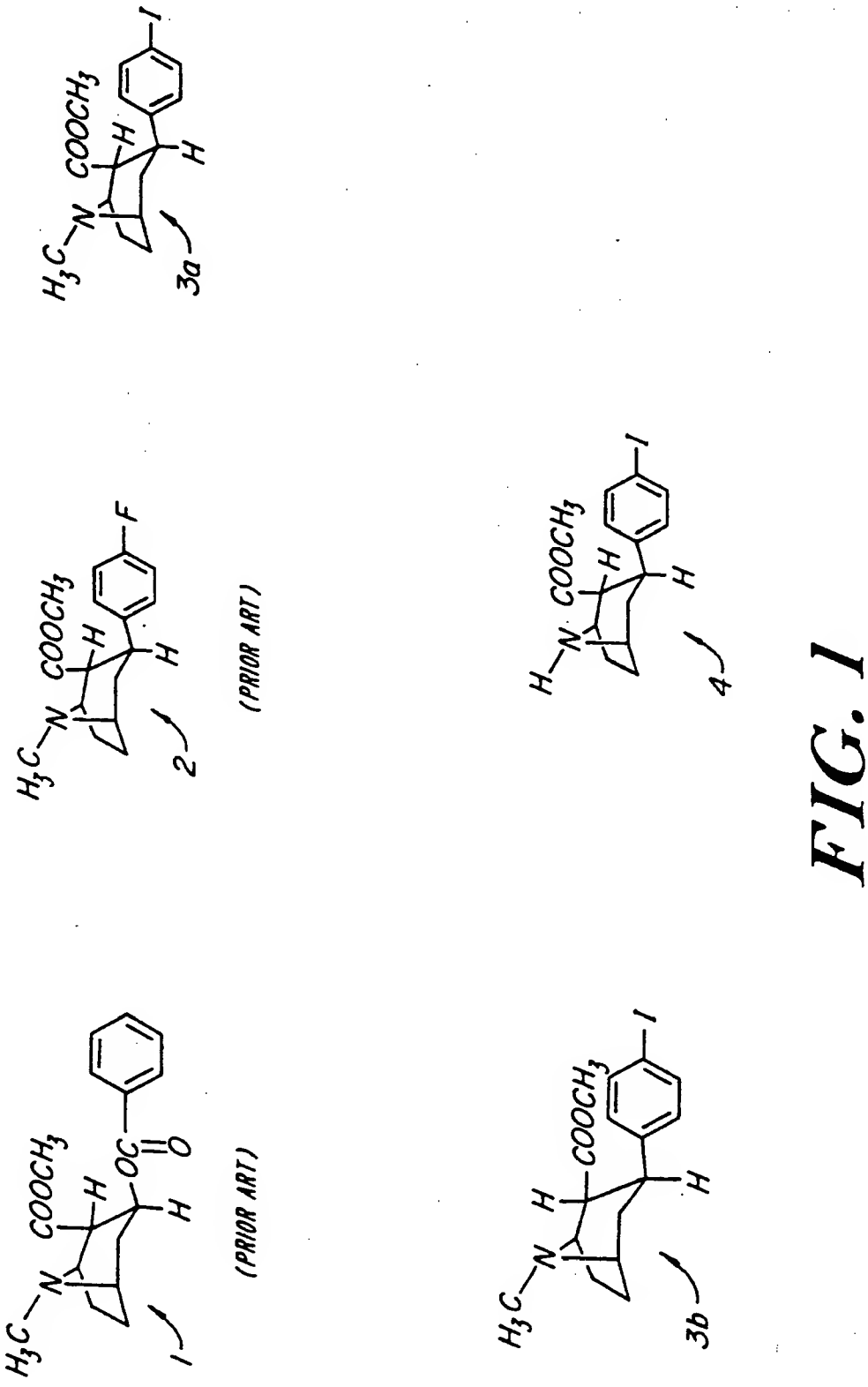


FIG. 1

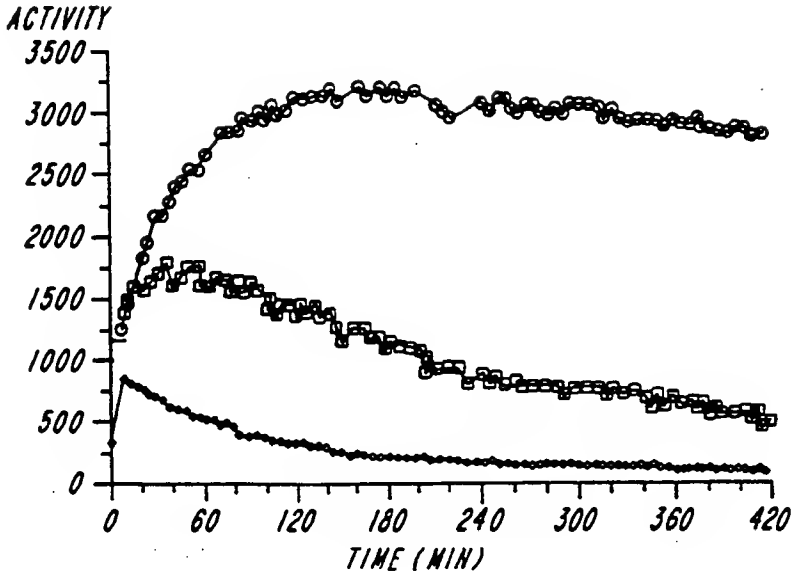


FIG. 2

REGION INFORMATION

NAME	ACTIVITY	AREA	MEAN
A) R. STRIATAL	249688	184	1357
B) L. STRIATAL	261096	184	1419
C) R. CORTICAL	27156	186	146
D) L. CORTICAL	33108	186	178

FIG. 4

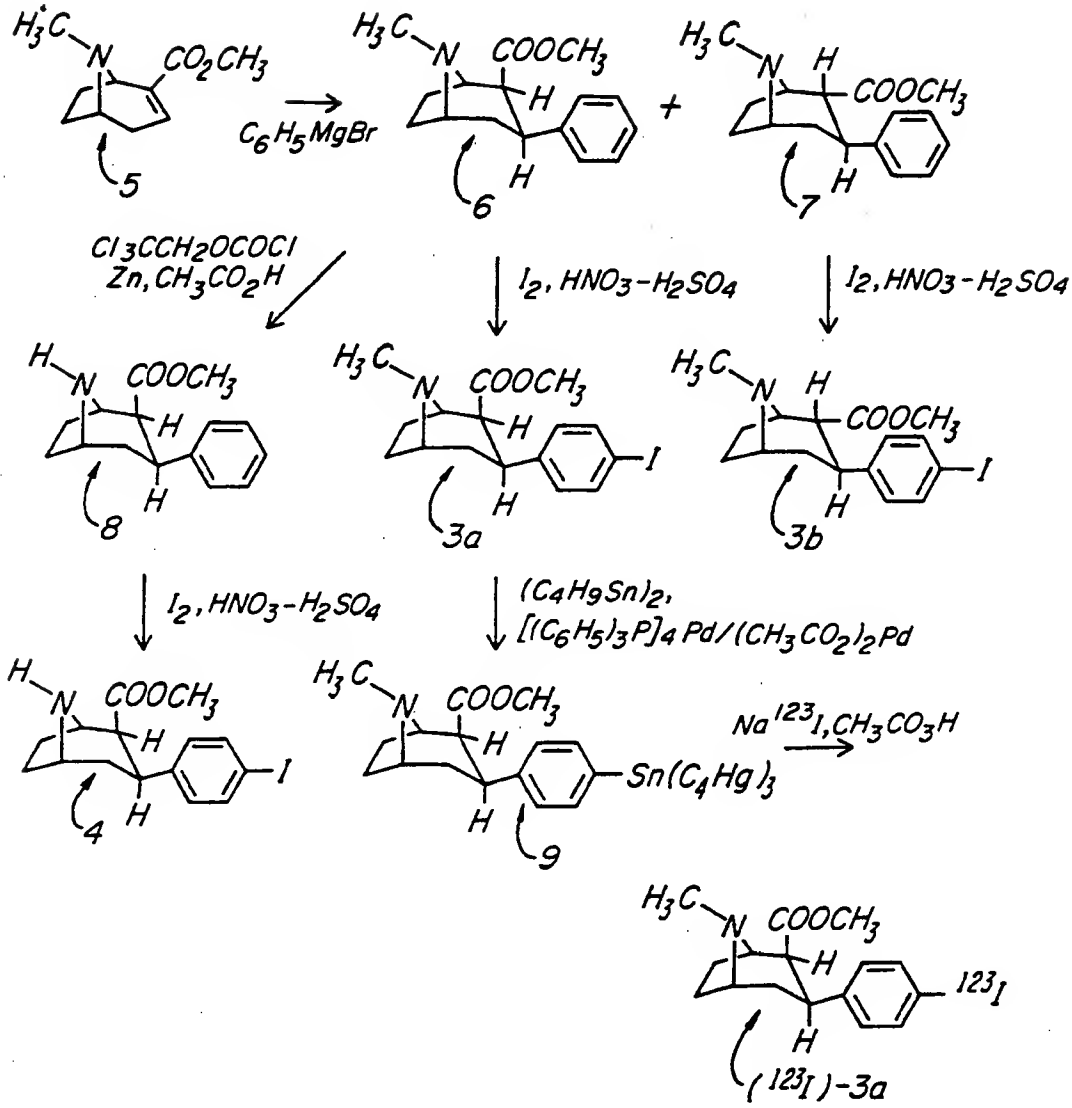

H3C
N
CO2CH3
5
C6H5MgBr
COOCH3
H
6
7
Cl3CCH2OCOCl
Zn, CH3CO2H
I2, HNO3-H2SO4
8
I
3a
3b
(C4H9Sn)2,
[(C6H5)3P]4 Pd/(CH3CO2)2Pd
4
Sn(C4Hg)3
9
Na 123I, CH3CO3H
123I
(123I)-3a

FIG. 3

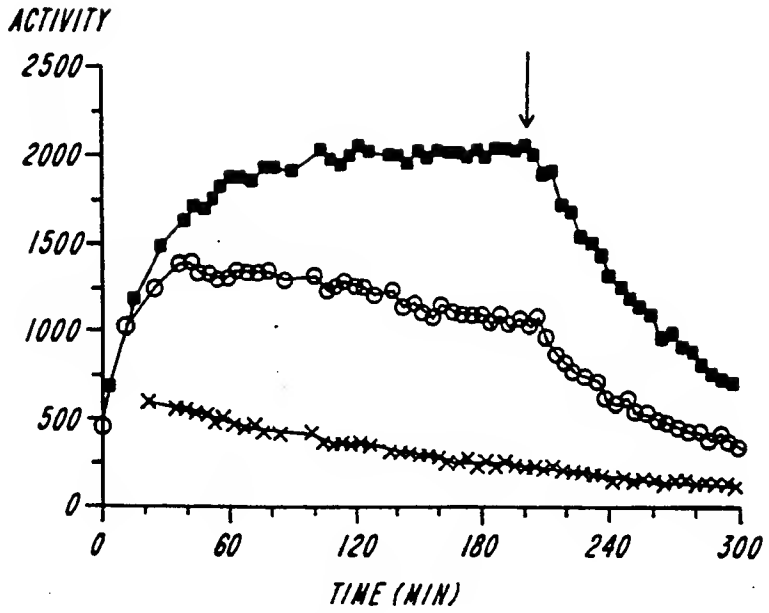

ACTIVITY
2500
2000
1500
1000
500
0
0
60
120
180
240
300
TIME (MIN)

FIG. 5A

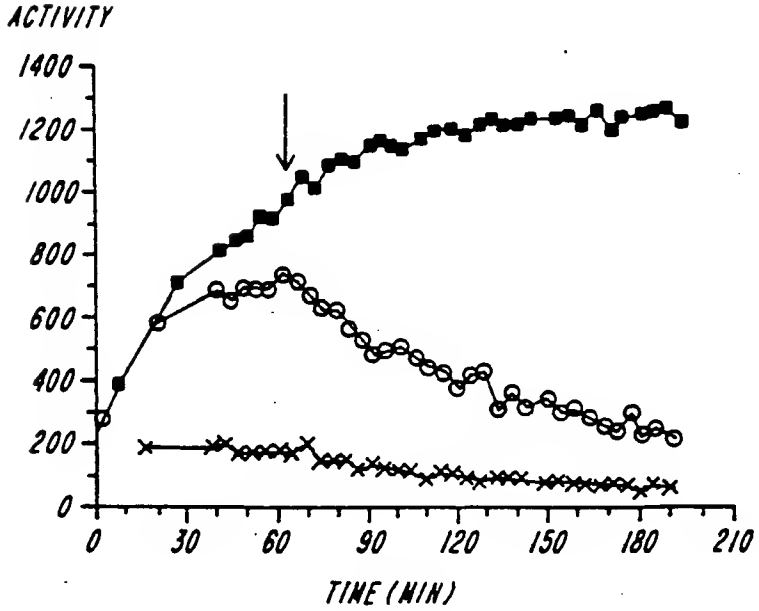

ACTIVITY
1400
1200
1000
800
600
400
200
0
0
30
60
90
120
150
180
210
TIME (MIN)

FIG. 5B

IODINATED NEUROPROBE FOR MAPPING MONOAMINE REUPTAKE SITES

FIELD OF INVENTION

This invention relates to neuroprobes for mapping monoamine reuptake sites in the brain, and particularly to a neuroprobe that can also serve as a radiotracer for use in single-photon emission computed tomography (SPECT) and positron emission tomography (PET) for imaging of such reuptake sites.

BACKGROUND OF THE INVENTION

A brain consists of a plurality of neurons that interact by exchanging chemical messengers. Each neuron generates neurochemicals, referred to as neurotransmitters; neurotransmitters act at sites on the cellular membrane of a neuron, the sites being referred to as receptors. Receptors are associated with either ion channels through the cellular membrane or secondary neurochemical messenger systems. By contrast, reuptake sites are molecular complexes which transport chemicals across the cellular membrane of a neuron. When a neurotransmitter has served its function, it is removed from the vicinity of the receptor by being bound to a reuptake site which transports the neurotransmitter to the interior of the neuron.

Just as there are many specialized neurons in the brain, there are also a variety of neurotransmitters, associated receptors, and reuptake sites. The distribution of specialized neurons depends upon the particular organism under study, and the state of health of that organism.

A neuron can be classified according to the type of neurotransmitter that it uses to communicate with other neurons. Certain types of neurons can be found predominantly in particular regions of the brain. For example, the striatal region of a mammalian brain is innervated by neurons using dopamine as a neurotransmitter. The striatum also contains a large number of non-dopaminergic neurons that have dopamine receptors. Certain compounds, such as cocaine, have a preferential affinity for dopamine reuptake sites, and therefore tend to bind to such reuptake sites. The effect of a molecule such as cocaine upon a dopamine reuptake site is to inhibit reuptake of the neurotransmitter dopamine, leaving more dopamine available in the vicinity of the dopamine receptors.

In certain neurological diseases, such as Parkinson's disease, distinct groups of neurons lose their normal physiological functioning. Consequently, the abnormal neurons may behave differently in the presence of some neurotransmitters, and may also produce neurotransmitters in a manner that differs from a healthy neuron.

The major neurotransmitters, dopamine, norepinephrine, and serotonin, are referred to collectively as the monoamine neurotransmitters. Many neurons have receptors adapted to receive at least one of these neurotransmitters. Parkinson's disease is caused by the degeneration of some of the dopaminergic neurons in the brain. The neurons lost in Parkinson's disease have a large number of dopamine reuptake sites; cocaine and chemical analogs of cocaine have an affinity for such reuptake sites.

A radioisotope is commonly incorporated in molecules that have a demonstrated binding affinity for a particular type of neuroreceptor, and such molecules are commonly used as neuroprobes. The localization of neuroprobes can be used to find specialized neurons within particular regions of the brain. It is also known that a neurological disease can be detected by observing abnormal binding distributions of a neuroprobe. Such abnormal binding distributions can be observed by incorporating a radionuclide within each molecule of the neuroprobe with a high binding affinity for the particular reuptake sites of interest. Then, an imaging technique can be used to obtain a representation of the in vivo spatial distribution of the reuptake sites of interest.

In single photon emission computed tomography (SPECT) imaging, the most commonly used radionuclides are heavy metals, such as ^{99m}Tc. Heavy metals are very difficult to incorporate into the molecular structure of neuroprobes because such probes are relatively small molecules (molecular weight less than 400).

In positron emission tomography (PET), the radiohalide ^{18}F (fluorine) is commonly used as a substitute for H (hydrogen) in radiopharmaceuticals because it is similar in size. Not all halogens will work, however. For example, I (iodine) is much larger than both H and F, being approximately half the size of a benzene ring. However, due to the small size of typical radiopharmaceuticals for use as neuroprobes, the presence of iodine markedly changes the size of the compound, thereby altering or destroying its biological activity.

In addition, the presence of iodine in a neuroprobe tends to increase its lipophilicity, and therefore increases the tendency of the neuroprobe to engage in non-specific binding For example, paroxetine is a drug with high affinity and selectivity for serotonin reuptake sites, and [^{3}H]paroxetine has been shown in rodents to be a useful in vivo label (Scheffel, U. and Hartig, PR. J. Neurochem., 52:1605–1612, 1989). However, several iodinated analogs of this compound with iodine attached at several different positions had unacceptably low affinity, in fact being one tenth of the affinity of the parent compound Furthermore, when the iodinated compound was used as an in vivo radiolabled neuroprobe, non-specific binding activity was found to be so high that no measurable portion of the brain uptake appeared to be specifically bound to the serotonin reuptake site. Thus, the iodinated form of paroxetine is not useful as an in vivo probe.

The addition of iodine to a neuroprobe can unfavorably alter its biological properties. For example, tomoxetine has high affinity and selectivity for norepinephrine reuptake sites. However, when tomoxetine is iodinated, e.g. to form R-4-iodotomoxetine, the resulting labeled compound has low affinity for such reuptake sites, and relatively high affinity for serotonin reuptake sites. In vivo labeling studies have shown that it is an unacceptably poor probe even for the serotonin reuptake sites because it exhibits low total brain uptake and immeasurably low specific uptake.

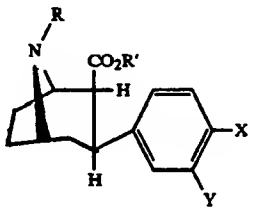
An iodinated compound can be useful as an in vitro probe, but may be useless as an in vivo probe, because an in vivo probe must meet the requirements associated with intravenous administration of the probe to a living subject. Reasons for the loss of in vivo utility include the fact that the compound may be metabolized too quickly, that it may not cross the blood-brain-barrier, and that it may have high non-specific uptake into the lipid stores of the brain. In vitro homogenate binding studies remove these obstacles by isolating the brain tissue from hepatic metabolic enzymes, by homogenizing the brain tissue so as to destroy the blood-brain-bar-

rier, and by diluting the brain tissue so as to decrease the concentration of lipids in the assay tube. Accordingly, it cannot be assumed that a probe will be useful in both in vivo and in vitro modalities.

An in vivo SPECT probe was developed by iodinating cocaine. However, this probe shows a binding affinity and specificity no better than cocaine itself, which is inadequate for purposes of SPECT imaging.

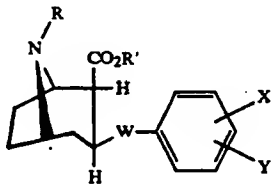
SUMMARY OF THE INVENTION

An iodinated neuroprobe is provided for mapping monoamine reuptake sites. The iodinated neuroprobe is of the formula:



wherein R can be a C_nH_{2n+1} group, where n=0–6, an alkenyl group, a monofluoroalkyl group including ^nF where n=18 or 19, or a $^mC_nH_{2n+1}$ group where n=1–6 and where m=11 or 14 for at least one ^mC. Also R′ can be a C_nH_{2n+1} group where n=0–6, a p-iodophenylmethyl group, a p-iodophenylethyl group, a phenylmethyl group, or a phenylethyl group. X can be an isotope of F, an isotope of Cl, an isotope of Br, an isotope of I, CH_3, or $Sn(R''_1R''_2R''_3)$. R''_1 can be a C_nH_{2n+1} group where n=1–6, or an aryl group. R''_2 can be a C_nH_{2n+1} group where n=1–6, or an aryl group. R''_3 can be a C_nH_{2n+1} group where n=1–6, or an aryl group. Y can be H only if X is an isotope of I, or R′ is a p-iodophenylmethyl group, or R′ is a p-iodophenylethyl group. Otherwise Y must be an isotope of I. Also provided is a diastereomer of this embodiment wherein the carboxyl-R′ group is in the alpha position.

In a further embodiment, the iodinated neuroprobe for mapping monoamine reuptake sites of the invention is of the formula:



wherein R can be a C_nH_{2n+1} group where n=0–6, an alkenyl group, a monofluoroalkyl group including ^nF where n=18 or 19, or a $^mC_nH_{2n+1}$ group where n=1–6 and where m=11 or 14 for at least one ^mC. R′ can be a C_nH_{2n+1} group where n=0–6, a p-iodophenylmethyl group, a p-iodophenylethyl group, a phenylmethyl group, or a phenylethyl group. X can be an isotope of F, an isotope of Cl, an isotope of Br, an isotope of I, CH_3, or $Sn(R''_1R''_2R''_3)$. R''_1 can be a C_nH_{2n+1} group where n=1–6, or an aryl group. R''_2 can be a C_nH_{2n+1} group where n=1–6, or an aryl group. R''_3 can be a C_nH_{2n+1} group where n=1–6, or an aryl group. Y can be H only if X is an isotope of I, or R′ is a p-iodophenylmethyl group, or R′ is a p-iodophenylethyl group. Otherwise, Y must be an isotope of I. Further, W can be O, S, $(CH_2)_n$, $O(CH_2)_n$ where n=1–6, wherein X resides on a benzene ring of the formula at an ortho, meta, or para position with respect to W, and Y resides at any remaining position on the benzene ring. Also provided is a further embodiment which is a diastereomer of this embodiment wherein the carboxyl-R′ group is in the alpha position.

For each of the foregoing embodiments there is provided a precursor of the radiolabled neuroprobe that lacks a radiotracer atom, and a kit for preparing an associated iodinated neuroprobe.

Both the radiostable and radioactive variants of the iodinated neuroprobe of the invention are useful for human and non-human research. For example, in vivo and in vitro experiments can be performed using the compounds of the invention to study dopamine reuptake sites generally, and cocaine binding sites in particular.

DESCRIPTION OF THE DRAWING

The invention will be more fully understood from the following detailed description, in conjunction with the accompanying figures in which:

FIG. 1 shows prior art compounds compared to compounds of the invention;

FIG. 2 shows regional activity in a baboon brain following injection of a compound of the invention;

FIG. 3 shows a synthesis route for a compound of the invention;

FIG. 4 shows regional areas of brain uptake of a compound of the invention;

FIG. 5A shows regional activity in a baboon brain following injection of compound of the invention; and

FIG. 5B shows regional activity in a baboon brain following injection of a compound of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Metabolically stable cocaine analogs such as 2β-carbomethoxy-3β-(4-iodophenyl)-tropane), an iodine-containing analog of β-CIT (also designated RTI-55), as shown in FIG. 1, compound 3, have high affinities for dopamine and serotonin reuptake sites in brain. As will be discussed below, [^{123}I]-β-CIT is shown to be a SPECT (single photon emission computed tomography) radiotracer for dopamine and serotonin reuptake sites.

[^{123}I]-β-CIT was prepared by reaction of the corresponding tributyltin precursor with no-carrier added Na[^{123}I] in the presence of peracetic acid, followed by preparative HPLC on a C-18 column with methanol/-water/triethylamine (75/25/0.2) at a flow rate of 1.0 ml/min. The final product was formulated in 6 ml sterile saline containing 5–10% ethanol.

Six SPECT experiments were performed in four female baboons (10 kg Papio anubis) under isoflurane anesthesia. The animals were injected with 10.6±1.4 mCi[^{123}I]-β-CIT and scanned for 333±25 min in either the 810X Brain Imager (Strichman Medical Equipment; five experiments) or the ASPECT device (Digital Sintigraphics, Cambridge, MA; one experiment), with these and subsequent data expressed as means ± S.E.M. Serial 2–6 min images were reconstructed assuming uniform attenuation equal to that of water in an ellipse drawn around the brain. Data were decay-corrected to the time of injection.

FIG. 2 illustrates regional activity in baboon brain following injection of 9.6 mCi [^{123}I]CIT. Activity is expressed in arbitrary units known from phantom studies to be linear with radioactive concentrations. The activities in three brain regions are graphed wherein the trace of open circles is the striatum, the trace of open squares is the midbrain, and the trace of open diamonds is the cerebellum.

The highest activities were found in the striatal region and reached peak levels at 179±9 min (n=6) post injection (p.i.)(FIG. 2). Striatal activity was monitored in two animals for an additional 190 and 260 min post peak values. In one animal, striatal activity was virtually unchanged for the remaining 190 min of the experiment. With reference to FIG. 2, in the second animal, washout of striatal activity was fit to an exponential function and had $T_{\frac{1}{2}}$=27 h (r=0.92).

The brain region which approximately overlay the mesencephalon or midbrain area had the second highest levels of activity. Midbrain values peaked earlier (45±16 min p.i ; n=6) and washed out more rapidly ($T_{\frac{1}{2}}$=294±59 min; r=0.98±0.01; n=3) than that in the striatum.

At the time of peak striatal uptake, the ratios of regional brain activities were: striatum (100%); hypothalamus (38.1±5.2%); occipital lobe (13.5±0.8%); temporo-parietal lobes (14.3±2.0%); frontal lobe (10.3±1.0%); and cerebellum (10.0±1.5%), all measured with n=6.

(−)Cocaine (FIG. 1, compound 1) and CFT (FIG. 1, compound 2), both potent dopamine and serotonin reuptake inhibitors, induced rapid and dose-dependant displacement of both striatal and midbrain activity. (−)Cocaine (2.9 μmol/kg) administered at 200 min p.i. caused displacement of 17% of striatal and 49% of midbrain levels within 30–65 min. At 14.7 μmol/kg administered at 230 min p.i., the corresponding cumulative displacements were 62% and 77%, respectively, within the same period of time.

CFT (0.4 μmol/kg) administered i.v. at 180 min p.i. caused displacement of 57% of striatal and 72% of midbrain levels within 60–120 min. At 2.0 μmol/kg administered at 298 min p.i., the corresponding cumulative displacements were 83% and 91%, respectively, within the same period of time.

In contrast, citalopram (a selective serotonin reuptake inhibitor) caused greater displacement of midbrain than striatal activity. At a dose of 8.3 μmol/kg i.v. at 190 min p.i., midbrain levels decreased by 57% during the following 110 min, compared to only 5% decrease in striatal activity during the same period.

[^{123}I]-β-CIT appears to be a useful SPECT tracer of the dopamine and serotonin reuptake sites. Brain uptake and washout are relatively slow in comparison to cocaine itself and are consistent with the metabolically resistant chemical structure of β-CIT and the location of the radioiodine in a chemically stable position. Striatal uptake appears to largely represent labeling of the dopamine reuptake site, whereas that in the midbrain is largely associated with the serotonin reuptake site. The high ratios of striatal to cerebellar activity of [^{123}I]-β-CIT are consistent with low non-specific uptake of the tracer, and suggest that [^{123}I]-β-CIT may be a useful clinical marker of dopaminergic deficiencies in Parkinson's disease.

Referring again to FIG. 1, in a second study (Neumeyer, J. L. et al., J. Med. Chem., 34:3144–3146, 1991), the potent cocaine analog 2β-carbomethoxy-3β-(4-fluorophenyl)tropane (compound 2) (also referred to as CFT or WIN 35,428 (Clarke, R. L., et al., 1973; Madras, B. K. et al., 1989)) when tritiated or labeled with $^{11}CH_3$ was found to be superior to [^{3}H]cocaine or [^{11}C]cocaine (Fowler, J. S. et al., Synapse 4:371–377, 1989) as a radioligand probe for cocaine receptors in terms of higher affinity and larger residence time on the dopamine reuptake site. For further development of analogues suitable for PET and SPECT imaging, 2β-carbomethoxy-3β-(4-iodophenyl)tropane were synthesized and characterized (compound 3a; designated as β-CIT in analogy to CFT, its corresponding, N-demethylated derivative (compound 4; designated as nor-CIT), and the C_{2a} isomer (compound 3b), as shown in FIG. 1.

Referring to FIG. 3, a synthesis protocol for [^{123}I]-β-CIT is described. Ecgonidine methyl ester (compound 5) was prepared from cocaine by the procedure of Clarke et al. (1973.) Treatment of compound 5 with phenylmagnesium bromide and subsequent workup with trifluoroacetic acid at low temperature gave a mixture of C_2 epimers (compound 6) (45%) and (compound 7) (31%), which were separated by flash chromatography (silica; CH_2Cl_2/CH_3OH, 25:1). Direct iodination of compound 6 with $I_2/HNO_3/H_2SO_4$ gave the para-substituted compound 3a (β-CIT) as an oil; 62%; $[\alpha]_{25}D$ −2.0° (c=0.85, $CHCl_3$). D-Tartrate salt; mp 72°–74° C.; $[\alpha]^{25}D$ −87.7° (c=1.5, CH_3OH). Iodination of compound 7 by the same procedure gave compound 3b (α-CIT) as an oil; 39% $[\alpha]^{25}D$ +44° (c=2.5, $CHCl_3$). 1,5-naphthalenedisulfonate salt; mp 139°–140° C. N-Demethylation of compound 6 was accomplished by conversion to its 2,2,2,-trichloroethyl carbamate followed by reduction (Zn/acetic acid) to yield compound 8 by the procedure previously described by Milius, R. A., et al., J. Med. Chem. Vol. 34, No. 5, 1728–1731, 1991, herein incorporated by reference, followed by iodination to yield nor-CIT (compound 4), which was isolated as a yellow crystalline solid (free base 48% from compound 6): mp 149°–151° C.; $[\alpha]^{25}D$ −67.4° (c=1, $CHCl_3$).

[^{123}I]-β-CIT (compound ^{123}I-3a) was synthesized from nonradioactive β-CIT (compound 3a) by conversion to the corresponding tributyltin derivative (compound 9). Treatment of compound 3a with bis(tributyltin), tetrakis(triphenylphosphate)palladium(O), and palladium(II) acetate in refluxing tetrahydrofuran gave compound 9 as a colorless waxy solid after flash chromatography (silica, stepwise gradient, hexane to hexane/ether, 75:25) in 26% yield from 3a. The 300-MH_3 NMR ($CDCl_3$) of compound 9 was consistent with the assigned structure. Reaction of compound 9 with no-carrier-added $Na^{123}I$ in the presence of peracetic acid gave compound [^{123}I]-3a. The radioiodinated product compound [^{123}I]-3a was purified by preparative HPLC (Novapak C_{18}, $MeOH/H_2O/Et_3N$, 75:25:0.2, 1.0 mL/min; t_R 6.7 min) and formulated in normal saline containing 5% ethanol an 1% ascorbic acid. Compound [^{123}I]-3a was obtained in average overall yield of 60.0 ±13.4% and with radiochemical purity of 97.6±1.6%. The tributyltin precursor used in radiolabeling contained about 7 mol % CIT carrier, resulting in an ^{123}I product having a specific activity of about 2000 ci/mmol.

The affinities of cocaine (compound 1), α-CIT (compound 3b), β-CIT (compound 3a), and β-CFT (compound 2) for the dopamine and serotonin reuptake sites were determined from radioligand displacement studies

using tissue homogenates prepared from baboon and rat brain, shown in Table 1 below.

TABLE I

In Vitro Radioligand Binding Data for Cocaine and 3-(4-Halophenyl) Analogues[a]

		displacement of [^{3}H]CFT		displacement of [^{3}H]paroxetine	
	analogue	IC_{50} (nM)	Hill slope (nH)	IC_{50} (nM)	Hill slope (nH)
1	(cocaine)	221 ± 14	0.69 ± 0.06 (3)	207 ± 66	0.73 ± 0.12 (5)
2	(β-CFT)	15.3 ± 1.2	0.75 ± 0.01 (3)	479 ± 59	1.34 ± 0.22 (3)
3b	(α-CIT)	87.6 ± 2.9	0.70 ± 0.07 (2)	210 ± 86	0.73 ± 0.04 (2)
3a	(β-CIT)	1.6 ± 0.15	0.79 ± 0.04 (3)	3.78 ± 0.53	0.82 ± 0.08 (6)

The data in Table 1 represent radioligand binding of [^{3}H]CFT (0.5 nM) to dopamine reuptake sites in tissue homogenates prepared from primate striatum and binding of [^{3}H]paroxetine to serotonin reuptake sites in homogenates prepared from rat cortical membranes. The IC_{50} value is the concentration of displacing analogue required to decrease specific radioligand binding by 50%. Values represent means ±SEM (of n experiments).

With reference to FIG. 4, five SPECT (single photon emission computer tomography) experiments were performed with four female baboons (Papio anubis, 10–12 kg) under isoflurane anesthesia. Animals were injected i.v with 8.1±1.4 mCi [^{123}I]-β-CIT (with these and subsequent data expressed as mean ± SEM) and scanned for 300±41 min with the 810X Brain Imager (Strichman Medical Equipment, Medfield, MA). Serial 1–2 min images were reconstructed assuming uniform attenuation equal to that of water in an ellipse drawn around the brain. Data were decay corrected to time of injection.

FIGS. 5A and 5B illustrate regional activity in baboon brain following iv injection of 12.1 mCi (FIG. 5A) and 4.2 mCi (FIG. 5B) [^{123}I]CIT. Activity is expressed in arbitrary units known from phantom studies to be linear with radioactive concentrations. Displacing agents (FIG. 5A: 13 μmol Lu-19-005 per kg; FIG. 5B: 7.4 μmol Citalopram per kg) were injected iv at the times marked with arrows. Activities in three brain regions are graphed wherein the trace of filled squares is the striatum, the trace of open circles is the midbrain, and the trace of Xs is the cerebellum.

Highest brain uptake overlay the striatal region and peaked at 154±19 min postinjection (pi) of the radioligand and showed striatal to cerebellar ratios at that time of 9.8±1.6. Washout of striatal activity was followed for an additional 200 and 260 min in two of three control animals and showed 0% and 12% decreases, respectively, from time of striatal peak to end of the experiment.

With reference to FIGS. 5A and 5B, the brain area with second highest activities approximately overlays the midbrain and showed peak levels at 43±5 min pi (n=5) and had a faster washout than striatal activity.

The pharmacological specificity of the in vivo labeling of [^{123}I]-β-CIT was examined with displacement of brain activity by indatraline (also designated Lu 19-005), a potent agent for the dopamine and serotonin reuptake sites, and citalopram, an agent selective for the serotonin reuptake site. Indatraline (3 μmol/kg iv) injected at 200 min pi radioligand caused significant decrease of both striatal and midbrain activity, as shown in FIG. 5A. During the 100 min period after injection of Lu 19-005, striatal activity decreased by 65% compared to a mean decrease of 2% during the same period in the two control animals followed for that length of time. In contrast, citalopram (7.4 μmol/kg iv) injected 60 min pi radioligand showed a selective decrease of midbrain activity, as shown in FIG. 5B. Citalopram caused a 48% decrease of midbrain activity during the 60-min period after injection, in comparison to 16±3% decrease (n=3) of midbrain activity in control animals followed during this same period.

These results showed that [^{123}I]-β-CIT was a useful SPECT probe of monoamine reuptake sites in primates. The majority of striatal activity was associated with dopamine reuptake sites, and the majority of midbrain activity was associated with serotonin reuptake sites, which is consistent with the densities of these monoamine transporters measured in postmortem primate brains. Brain washout of activity was relatively slow, in part because of the high affinities of β-CIT for the monoamine transporters. In addition, the iodine atom appears to be in a relatively metabolically resistant position, since whole body scanning showed low thyroid uptake, which is indicative of a slow in vivo rate of deiodination. [^{123}I]-β-CIT and [^{11}C]-β-CIT may be useful clinical markers of dopaminergic and serotonergic innervation in human disorders such as Parkinson's disease and depression, which are thought to have abnormalities in these neuro-transmitter systems.

EXAMPLES OF SYNTHESES

EXAMPLE 1

2-beta-Carbomethoxy-3-beta-(4-iodophenyl)tropane

A mixture of 2-beta-carbomethoxy-3-beta-phenyltropane (See Example 1A below and Milius et al. J. Med. Chem., 1991, 34, 1728) (2.9 g, 11.5 mmol) and I_2 (3 g. 11.8 mmol) in 25 ml of glacial acetic acid was stirred and treated dropwise with a mixture of 4.7 mL of concentrated nitric acid and 4.7 mL of concentrated sulfuric acid. The reaction mixture was heated to 55° C. and stirred for 2 hours, then cooled to room temperature and poured onto ice (100 g) and filtered. The pH of the filtrate was adjusted to 9.5 by the addition of concentrated ammonium hydroxide at 0°–5° C. The resulting precipitate was removed by filtration and dissolved in methylene chloride (250 ml). The filtrate was extracted with two 50 mL portions of methylene chloride. The extracts and solution of precipitate were combined, washed with brine (50 ml) and dried over magnesium sulfate. After the removal of the solvent, 3.9 g (90.4%) of 2-beta-carbomethoxy-3-beta-4-iodophenyltropane free base was obtained as an oil.

The free base was dissolved in methanol (20 ml) and combined with 1.5 g of D-(-)tartaric acid in 20 ml of methanol. After the removal of methanol under reduced pressure, the residue was recrystallized from methanol ether (3:1) to give 2-beta-carbomethoxy-3-beta-(4-iodophenyl)tropane D-tartrate salt as white crystals, m.p. 72°–74° C. $C_{16}H_{20}NO_2I.C_4H_6O_6$. Calcu-

lated: C: 44.88, H: 4.89, N: 2.62. Found: C: 44.70, H: 4.94, N: 2.57. [alpha]$_D^{22}$ = −87.7° (c=0.3, CH_3OH).

EXAMPLE 1A

2-beta-Carbomethoxy-3-beta-phenyltropane

A 2M ethereal solution of phenylmagnesium bromide (83 mL, 166 mmol) in a 500-mL 3-neck round-bottom flask equipped with mechanical stirrer, addition funnel, and nitrogen inlet tube was diluted with 83 mL of anhydrous diethyl ether and cooled to −20° C. under an atmosphere of dry nitrogen. A solution of anhydroecgonine methyl ester, prepared from cocaine (1) (15 g, 82.8 mmol) in anhydrous ether (75 mL) was added dropwise. The heterogeneous mixture was stirred for 1 h at −20° C., then poured into an equal volume of ice and water, and acidified by the dropwise addition of 2M HCl. The aqueous layer was made basic by the addition of concentrated ammonium hydroxide, saturated with NaCl, and extracted with diethyl ether. The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to give a brown oil. Bulb to bulb distillation (70° C., 0.9 Torr) of the crude product gave a pale yellow oil (16 g, 70%). TLC analysis of the oil (silica, pentane/-diethyl ether/2-propylamine, 15:5:0.8) showed it to be a mixture of the C-2 alpha and beta epimers. The beta isomer was isolated by silica gel chromatography (pentane: diethyl ether: isopropyl amine, 70:30:3). m.p. 63°–66° C. (lit: 62–64,5° C.: Clarke et al. J. Med. Chem.. 16:1260 (1973)).

EXAMPLE 2

2-alpha-Carbomethoxy-3-beta-iodophenyltropane

The mixture of alpha and beta-2-carbomethoxy-3-beta-iodophenyltropanes prepared as described in Example 1 were separated by silica gel chromatography as described in Example 1. Fractions containing the alpha-2-carbomethoxy-3-beta-iodophenyltropane were pooled and concentrated in vacuo. The free base thus obtained was treated with naphthalene-1,5-disulfonic acid. The crude salt was recrystallized from acetonitrile to give the 2-alpha-carbomethoxy-3-beta-iodophenyltropane naphthalene-1,5-disulfonate salt, m.p. 166°–168° C. $C_{16}H_{20}NO_2I.C_{10}H_6(SO_3H)_2.2H_2O$. Calculated: C:40.01, H:4:55, N:1.97, I:17.90; Found: C:43.94, H:4.55, N:1.91, I:17.99.

EXAMPLE 3

2-beta-Carbomethoxy-3-beta-(4-iodophenyl)nortropane.

A solution of 2-beta-carbomethoxy-3-beta-(4-iodophenyl)tropane (410 mg, 1.5 mmol) in toluene (20 mL) was treated with of 2,2,2-trichloroethyl chloroformate (1 mL, 7.3 mmol). The mixture was heated at 120° C. for 1 hour, cooled to room temperature, and evaporated to dryness in vacuo. The residue was partitioned between methylene chloride and water. The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo to give the trichloroethyl chloroformate as a dry foam. The crude carbamate was dissolved in 50% aqueous acetic acid, treated with 200 mg (0.0067 g-atom) of zinc dust, and stirred at room temperature for 16 hours. The reaction mixture was filtered adjusted to pH 7 with concentrated ammonium hydroxide, saturated with NaCl, and extracted with diethyl ether. The extracts were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography (silica, pentane/diethyl ether/isopropylamine, 3:7:0.7) to afford 2-beta-carbomethoxy-3-beta-(4-iodophenyl)nortropane, which was isolated as a yellow crystalline solid, m.p. 149°–151° C.; [alpha]$^{25}_D$−67.4° (c=1, $CHCl_3$).

EXAMPLE 4

2-beta-Carbomethoxy-3-beta-(4-iodophenyl)-8-(3-fluoropropyl)-nortropane

A solution of 2-beta-carbomethoxy-3-beta-(4-iodophenyl)-nortropane (371 mg, 1.0 mmol), 1-bromo-3-fluoropropane (155 mg, 1.1 mmol), and triethylamine (0.5 mL) in dry toluene (20 mL) was stirred under an atmosphere of dry nitrogen and heated to reflux. After four hours, the reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure, and the residue chromatographed on a silica column (eluant: diethyl ether). Concentration of product-containing fractions gave 2-beta-carbomethoxy-3-beta-(4-iodophenyl)-8-(3-fluoropropyl)nortropane as a white solid, m.p. 78.5°–79.5° C. $C_{18}H_{23}NO_2FI$, Calculated: C: 50.13, H:5.34, N: 3.25; Found: C: 50.27, H: 5.26, N:3.15.

EXAMPLE 5

2-beta-Carbomethoxy-3-beta-(3-fluoro-4-iodophenyl)-tropane

A mixture of 2-beta-carbomethoxy-3-beta-(3-fluorophenyl) tropane (400 mg, 1.44 mmol), silver sulfate (400 mg, 1.3 mmol), iodine (600 mg, 2.36 mmol) and 80% sulfuric acid (9 Ml) was stirred for five days at room temperature. The reaction mixture was poured into 150 mL of ice and water, made basic by the addition of concentrated ammonium hydroxide, and extracted with three 60 mL portions of chloroform. The combined extracts were washed sequentially with solutions of 10% sodium bisulfite, 5% sodium carbonate and water, then dried over sodium sulfate, and filtered. The filtrate was concentrated in vacuo and the oily residue was redissolved in chloroform and treated with a solution of p-toluene sulfonyl chloride in chloroform. The resulting solid was repeatedly recrystallized from water and ethanol to give 2-beta-carbomethoxy-3-beta-(3-fluoro-4-iodophenyl)tropane tosylate salt as a white crystalline solid, m.p. 68°–70° C. (soften, 45° C.), $C_{16}H_{19}FINO_2 \cdot C_7H_8SO_3 \cdot H_2O$: Calculated: C: 46.55,H: 4.93, N: 2.36; Found: C: 46.34, H: 4.86, N:1.99.

EXAMPLE 6

2-beta-Carboxy-3-beta-(4-iodophenyl)tropane

A suspension of 2-beta-carbomethoxy-3-beta-(4-iodophenyl)tropane (100 mg, 0.26 mmol) in 2 mL of H_2O was heated at reflux for 10 hours. The resulting solution was cooled to room temperature, and the resulting precipitate was collected by filtration and dried under vacuum overnight to give 70 mg (70%) of 2-beta-carboxy-3-beta-(4-iodophenyl)tropane m.p. 299°–300° C. $C_{15}H_{18}NO_2I.0.5\ H_2O$: Calculated C: 47.51, H:5.05, N: 3.69: Found: C: 47.28, H: 4.84, N: 3.69.

EXAMPLE 7

2-beta-Carbomethoxy-3-beta-benzyloxytropane

A stirred suspension of benzyl bromide (3.0 g, 0.015 mol) and potassium iodide (3.0 g, 0.021 mol) in acetone (20 mL) was treated dropwise with a solution of ecgonine methyl ester (2.6 g, 0.014 mol) in acetone (10 mL) at room temperature. The mixture was stirred at room

temperature for 70 hours, then heated to reflux and stirred for an additional 8 hours. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated in vacuo, the residue dissolved in chloroform (200 mL) and extracted with four 50 mL portions of 2N hydrochloric acid. The combined extracts were made basic by the addition of concentrated ammonium hydroxide. The resulting mixture was extracted with four 20 mL portions of chloroform. The extracts were dried over sodium sulfate and concentrated in vacuo to give 1.7 g of 2-beta-carbomethoxy-3-beta-benzyloxytropane as an oil.

The product was dissolved in acetonitrile (20 mL) and treated with a solution of naphthalene-1,5-disulfonic acid (2.2 g) in acetonitrile (20 mL). The solution was concentrated in vacuo to a syrup, which was diluted with diethyl ether. The resulting precipitate was collected by filtration and dried to give 1.6 g of 2-beta-carbomethoxy-3-beta-benzyloxytropane naphthalene-1,5-disulfonate salt, m.p. 126°–130° C., $C_{17}H_{23}NO_3.C_{10}H_6(SO_3H)_2.2.5\ H_2O$. Elemental analysis: Calculated, C: 52.08, H: 5.83, N: 2.25. Found, C: 52.02, H: 5.69, N: 2.72. $[alpha]_D^{24} = -25.4°$ (c=1, CH_3OH).

EXAMPLE 8

2-beta-Carbomethoxy-3-beta-(4-tributylstannylphenyl)-tropane

A mixture of 2-beta-carbomethoxy-3-beta-(4-iodophenyl)tropane (250 mg, 0.65 mmol), bis(tributyl)distannane (522 mg, 0.9 mmol), tetrakis(triphenylphosphine)-palladium(O) (3 mg) and anhydrous toluene (10 mL) was heated to reflux under an atmosphere of dry nitrogen and stirred for 28 hours. The mixture was filtered, and the filtrate concentrated in vacuo. The residue was applied to a silica gel column and eluted with a mixture of hexane : diethyl ether : isopropyl amine (70:30:3). The fractions containing product were pooled, concentrated in vacuo and treated with pentane to precipitate 2-beta-carbomethoxy-3-beta-(4-tributylstannylphenyl)-tropane as a solid. The 300 MHz NMR spectrum was consistent with the assigned structure. $[alpha]_D^{22} = -8.9°$ (c=0.4, $CHCl_3$).

EXAMPLE 9

[^{123}I]-2-beta-Carbomethoxy-3-beta-(4-iodophenyl)tropane

To a vial containing 50 μg (0.094 μmol) of 2-beta-carbomethoxy-3-beta-(4-tributylstannylphenyl)tropane was added 50 μL ethanol, 150 μL 0.5M H_3PO_4, 125–500 μL (20–30 mCi) [^{123}I]NaI solution, and 100 μL (4.2 μmol) 0.042M peracetic acid. After 20–30 minutes, 50 μL of 100 mg/mL aqueous $NaHSO_3$ solution was added. Saturated $NaHCO_3$ solution was added, and the mixture extracted with ethyl acetate. The combined extracts were dried (Na_2SO_4) and concentrated to dryness. The residue was redissolved in methanol and purified by HPLC (C-18 column, eluant: CH_3OH: H_2O: triethylamine; 75:25:0.2). The fraction eluting at the retention time of 2-beta-carbomethoxy-3-beta-(4-iodophenyl)tropane was collected evaporated to dryness and reconstituted in 5% ethanol and 0.1 nM ascorbic acid.

In SPECT applications, the radiostable iodinated neuroprobe of the invention is useful as a reference standard, and can also be used as a dilutant for the radioactive form of the neuroprobe. The radioiodinated compound is generally identified by its chromatographic mobility as compared with a fully characterized reference standard. Thus, preparation of the radioiodinated compound requires the non-radioactive iodinated compound.

To avoid the necessity of storing a radioactive neuroprobe, it is useful to provide a kit containing the non-radioactive iodinated compound and an appropriate oxidizing agent, such as perchloric acid, performic acid, peracetic acid, hydrogen peroxide, hydrogen peroxide with lactoperoxidase, 1,3,4,6-tetrachloro-3α,6α-diphenylglycouril, or a N-chloro-4-methylbenzenesulfonamide sodium salt. Then, the non-radioactive precursor compound can be oxidized in the presence of a suitable radioactive compound, such as the carrier free Na[^{123}I] shown in the synthesis route described herein, any other radioisotope source, such as any solution of a salt of a radioactive isotope of iodine, a reagent containing $^{m}C_nH_{2n+1}X$, where n=0–6 and X is a leaving group, or a reagent containing ^{18}F of the formula $FC_nH_{2n}X$, where n=0–6 and X is a leaving group, to prepare the iodinated neuroprobe at its time and place of use.

Radiolabled neuroprobes of the invention are also useful in other imaging procedures. For example, an ^{125}I-labled neuroprobe can be used in autoradiography or therapy, and an ^{131}I-labled neuroprobe is useful as a multiple photon emitter for use in animal studies. Also, ^{11}C-, ^{14}C-, and ^{18}F-labeled neuroprobes can be used in PET imaging.

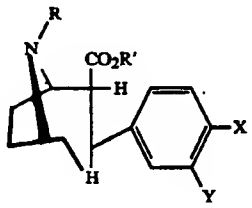
Both the radiostable and radioactive variants of the iodinated neuroprobe of the invention are useful for human and non-human research. For example, in vivo and in vitro experiments can be performed using the compounds of the invention to study the dopamine transporter generally, and cocaine binding sites in particular.

Additionally, the radiostable version of the neuroprobe of the invention can be used as a drug for influencing dopamine reuptake.

Other modifications and implementations will occur to those skilled in the art without departing from the spirit and the scope of the invention as claimed. Accordingly, the above-description is not intended to limit the invention except as indicated in the following claims.

What is claimed is:

1. An iodinated neuroprobe for mapping monoamine reuptake sites, the iodinated neuroprobe being of the formula:



wherein

R=a monofluoroalkyl group including ^{n}F where n=18 or 19;

R'=a C_nH_{2n+1} group where n=0–6;

X=an isotope of F, an isotope of Cl, an isotope of Br, an isotope of I, CH_3, or $Sn(R''_1R''_2R''_3)$;

R''_1=a C_nH_{2n+1} group where n=1–6, or an aryl group;

R''_2=a C_nH_{2n+1} group where n=1–6, or an aryl group;

R''_3=a C_nH_{2n+1} group where n=1–6, or an aryl group; and

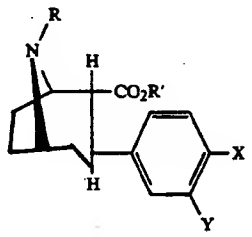
Y=H.

2. The iodinated neuroprobe of claim 1 wherein $X=^{123}I$.

3. The iodinated neuroprobe of claim 1 wherein $X=^{125}I$.

4. The iodinated neuroprobe of claim 1 wherein $X=^{131}I$.

5. An iodinated neuroprobe for mapping monoamine reuptake sites, the iodinated neuroprobe being of the formula:



wherein

R=a monofluoroalkyl group including ^nF where n=18 or 19;

R'=a C_nH_{2n+1} group where n=0–6;

X=an isotope of F, an isotope of Cl, an isotope of Br, an isotope of I, CH_3, or $Sn(R''_1R''_2R''_3)$;

R''_1=a C_nH_{2n+1} group where n=1–6, or an aryl group;

R''_2=a C_nH_{2n+1} group where n=1–6, or an aryl group;

R''_3=a C_nH_{2n+1} group where n=1–6, or an aryl group;

Y=H.

6. The iodinated neuroprobe of claim 5 wherein $X=^{123}I$.

7. The iodinated neuroprobe of claim 5 wherein $X=^{125}I$.

8. The iodinated neuroprobe of claim 5 wherein $X=^{131}I$.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

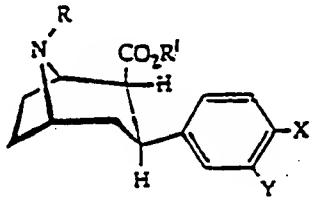
PATENT NO. : 5,310,912

DATED : May 10, 1994

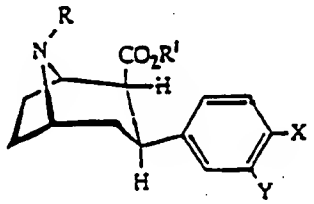
INVENTOR(S) : John L. Neumeyer, et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page, item [57], col. 2,
In the Abstract, the structure is not printed in accordance with the application. A carbon atom is missing in the tropane ring moiety. The correct structure is:



In Column 12, lines 52-62, the structure is not printed in accordance with the application. There is a carbon atom missing in the tropane ring, and 2 bonds are made to a hydrogen atom. The correct structure is:



UNITED STATES PATENT AND TRADEMARK OFFICE

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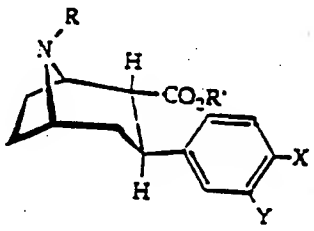
PATENT NO. : 5,310,912

DATED : May 10, 1994

INVENTOR(S) : John L. Neumeyer, et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 14, lines 1-12, the structure is not printed in accordance with the application. It is unclear that the tropane ring contains 7 carbon atoms. The correct structure is:



Signed and Sealed this

Third Day of January, 1995

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

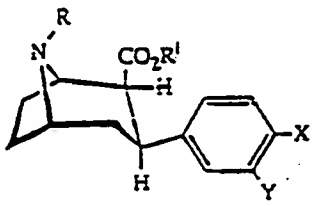
PATENT NO. : 5,310,912

DATED : May 10, 1994

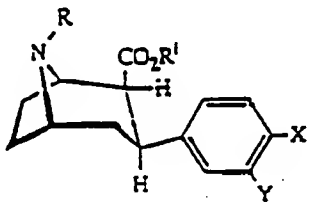
INVENTOR(S) : John L. Neumeyer, et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page, item [57], col. 2,
In the Abstract, the structure is not printed in accordance with the application. A carbon atom is missing in the tropane ring moiety. The correct structure is:



In Column 12, lines 52-62, the structure is not printed in accordance with the application. There is a carbon atom missing in the tropane ring, and 2 bonds are made to a hydrogen atom. The correct structure is:



UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

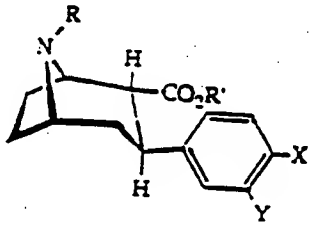
PATENT NO. : 5,310,912

DATED : May 10, 1994

INVENTOR(S) : John L. Neumeyer, et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 14, lines 1-12, the structure is not printed in accordance with the application. It is unclear that the tropane ring contains 7 carbon atoms. The correct structure is:



Signed and Sealed this

Third Day of January, 1995

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

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Patent Bibliographic Data

03/02/2011 11:54 AM

Patent Number:	5310912		**Application Number:**	07841617	
Issue Date:	05/10/1994		**Filing Date:**	02/25/1992	
Title:	IODINATED NEUROPROBE FOR MAPPING MONOAMINE REUPTAKE SITES				
Status:	4th, 8th and 12th year fees paid			**Entity:**	Large
Window Opens:	N/A	**Surcharge Date:**	N/A	**Expiration:**	N/A
Fee Amt Due:	Window not open	**Surchg Amt Due:**	Window not open	**Total Amt Due:**	Window not open
Fee Code:					
Surcharge Fee Code:					

Most recent events (up to 7):	11/10/2005	Payment of Maintenance Fee, 12th Year, Large Entity.
	12/19/2001	Refund - Payment of Maintenance Fee, 8th Yr, Small Entity.
	12/19/2001	Pat Hldr no Longer Claims Small Ent Stat
	12/10/2001	7.5 yr surcharge - late pmt w/in 6 mo, Large Entity.
	12/10/2001	Payment of Maintenance Fee, 8th Year, Large Entity.
	10/27/1997	Payment of Maintenance Fee, 4th Yr, Small Entity.
		--- End of Maintenance History ---
Address for fee purposes:	WEINGARTEN, SCHURGIN, GAGNEBIN & HAYES TEN POST OFFICE SQUARE BOSTON, MA 02109	

Run Another Query

E

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022454Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	January 5, 2011
From	Dwaine Rieves, MD
Subject	Division Director Summary Review
NDA/BLA #	22-454
Applicant Name	GE Healthcare
Date of Submission	November 16, 2010
PDUFA Goal Date	January 14, 2011
Proprietary Name / Established (USAN) Name	DaTscan™ Ioflupane I 123 Injection
Dosage Forms / Strength	DaTscan is supplied in 10-mL glass vials containing 2.5 mL of solution; each mL contains 0.07 to 0.13 mcg ioflupane, 74 MBq (2 mCi) of iodine 123 as ioflupane I 123 at calibration time along with defined excipients. The recommended dose is 111 to 185 MBq (3 to 5 mCi) administered intravenously.
Proposed Indication(s)	DaTscan is a radiopharmaceutical indicated for striatal dopamine transporter visualization using single photon emission computed tomography (SPECT) brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes (PS). In these patients, DaTscan may be used to help differentiate essential tremor from tremor due to PS (idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy). DaTscan is an adjunct to other diagnostic evaluations.
Action/Recommended Action:	Approval/a postmarketing study (PMC) to assess: agreement of image results with clinical diagnoses following 3 years of follow-up among African-American patients with clinically uncertain Parkinsonian syndromes (PS).

Importantly, this is the third review cycle for this application. The original submission was on March 6, 2009 and a Complete Response letter was issued on September 8, 2009 (deficiencies related to need for package insert labeling update). The second review cycle began with the applicant's resubmission on October 26, 2009 and concluded with issuance of a Complete Response letter on December 22, 2009 in which the single deficiency related to the need to incorporate Controlled Substance text in the package insert. The reviews cited below pertain predominantly to the original cycle review period.

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Phillip Davis, MD & Louis Marzella, MD, PhD (TL)
Statistical Review	Mark Levenson, PhD & Jyoti Zalkikar, PhD (TL)
Pharmacology Toxicology Review	Sunday Awe, PhD & Adebayo Laniyonu, PhD (TL)
CMC Review/OBP Review	Ravindra Kasliwal, PhD & Eldon Leutzinger, PhD
Microbiology Review	Bryan Riley, PhD
Clinical Pharmacology Review	Christy John, PhD & Y. Moon Choi, PhD (TL)
DDMAC	Michelle Safarik, PA-C
DSI	Lauren Iacono-Connors, PhD & Tejashri Purohit-Sheth, MD
CDTL Review	Louis Marzella, MD, PhD
OSE/DMEPA	Denise Baugh, PharmD & Todd Bridges, PharmD (TL)
OSE/DDRE	Kathryn O'Connell, MD, PhD & Claudia Karwoski, PharmD
Pediatric and Maternal Health	Jeanine Best, MSN, RN & Karen Feibus, MD (TL)
Project Manager	James Moore, PharmD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader
TL = Team Leader
CMC = chemistry, manufacturing and controls

1. Introduction:

On March 6, 2009, GE Healthcare submitted a New Drug Application (NDA) to support the marketing of DaTscan™ (^{123}I-ioflupane), a radiopharmaceutical imaging agent proposed for use in visualizing dopamine transporter protein (DAT) in the brain.

The current submission is the third review cycle for the drug, as outlined above. With the notification from DMEPA today that the proprietary name is acceptable and the container labels appropriate, all review concerns have been resolved. The overall regulatory background is notable for the following items:

During the original cycle:

- The application was assigned a priority review (as supported by neurologic consultation);

- The three DaTscan phase 3 studies had several atypical features which were discussed at an advisory committee that was held on August 11, 2009; the committee voted 11 to 2 to support a favorable risk to benefit determination for the drug;

- At least one phase 3 study (study 304) provided data sufficient to describe performance characteristics (strengths and limitations);

- The other two phase 3 studies provided collaborative findings;

- The overall DaTscan development program importantly contributed to the clinical assessment of the drug's efficacy in that:

  -*in vitro* autoradiography of human tissue confirmed DaTscan binding to DAT,

  -imaging "reads" were standardized as negative or positive in phase 3 studies in a manner proposed for market use,

  -imaging "reads" pertained to standard hot-spot anatomical visualization; specifically the radioisotope outlined the striatum as a readily recognizable anatomical structure,

  -imaging "reads" were read consistently among independent readers,

  -imaging read methods could be readily described in the package insert.

- No chemistry/manufacturing issues were identified during the original review cycle and all disciplines regarded the application as approvable except for statistics.

- The statistical reviewer did not regard the phase 3 study data as statistically persuasive to support approval of the drug;

- I agreed with the advisory committee and the clinical team that the totality of the nonclinical and clinical data were sufficient to support approval of DaTscan to assist in the evaluation of certain patients (as described in the final indication);

- A Complete Response letter was issued due to inability to resolve package insert text prior to the cycle termination date. Deficiencies pertained only to labeling.

During the second review cycle:

- The sponsor sufficiently responded to the labeling items identified at the conclusion of the original review cycle.

- Further review determined that DaTscan needed labeling modification to identify it as a schedule II narcotic because the active moiety is a derivative of cocaine. The review team acknowledged the sponsor's contention that abuse was not a

realistic consideration based upon the DaTscan dose, its presentation as well as its need to be handled by nuclear pharmacists.

- [redacted] (b)(5)

- A Complete Response letter was issued based solely upon the need to have controlled substance text incorporated in the labeling.

During the current review cycle:

- The resubmission contains the proposed labeling (revised package insert and container labels), a safety update (no notable safety concerns are reported from non-USA post-marketing experience and an ongoing study), a copy of the non-USA labeling, a response to the previous two FDA requests for post-marketing studies (these two studies were not requirements and the sponsor's response is outlined below).

- The sponsor incorporates all requested labeling text, including the controlled substance information. As of today, all outstanding issues have been resolved.

- The sponsor proposes a survey-type of post-marketing commitment study to help estimate DaTscan performance characteristics among non-Caucasians (a population with very limited representation within the overall NDA database) and to compare the results for Caucasians. This survey-type proposal is based, in large, part upon feasibility considerations due to reports of a lower prevalence of Parkinsonian symptoms among non-Caucasians.

  -final clinical protocol submission date: December 31, 2011
  -clinical trial completion date: April 30, 2013
  -final trial report submission date: July 31, 2013

- The sponsor justified not performing a post-marketing study to examine the effect of Parkinsonian therapies upon DaTscan images. The justification included summary data that verified no effect of drugs commonly used to treat Parkinsonian symptoms.

- [redacted] (b) (5) we plan to recommend approval of DaTscan as a controlled drug. All other issues have been resolved/the labeling describes the currently controlled nature of the drug.

Below is text largely excerpted from my original review memorandum.

During the original review, multiple findings necessitated modification of the proposed indication to that listed in the boxed header (at the top of this document). For example,

data were not available to verify that DaTscan imaged "functional neurons." Additionally, the review disclosed multiple data limitations within the three confirmatory clinical studies. For example, Study 304 (the most informative study) was extensively modified (10 protocol amendments) that fundamentally changed its original design. The other two clinical studies (301 and 003) had even more deficits. Nevertheless, Study 304 data were particularly strong in terms of the ability of the study to compare DaTscan image results to a reliable clinical diagnosis (based upon 3 years of follow-up after the DaTscan image). Additionally, the preclinical data were indisputable in terms of supporting the contention that DaTscan bound specifically to the human dopamine transporter (DaT) protein in the striatum.

The preclinical and clinical review teams supported approval of DaTscan. The statistical team pointed out the lack of statistical robustness within the confirmatory studies such that they regarded these studies as insufficient to support approval. The Advisory Committee voted 11 to 2 in support of a favorable risk-benefit profile for the drug. Overall, I regard the totality of data (particularly preclinical data and Study 304) as providing an acceptable risk-benefit profile for marketing. Post-marketing commitments were sought to obtain data from African Americans receiving DaTscan and to assess the potential interference with DaTscan imaging by dopaminergic drugs. As noted above the sponsor has supplied summary data indicating that commonly used anti-Parkinsonian drugs do not importantly change DaTscan results.

The indication for DaTscan ultimately reflected the strength of the supplied preclinical and clinical data. DaTscan may serve a particularly useful role in the evaluation of patients with clinically uncertain Parkinsonian Syndromes (PSs). PS have been associated with decreased dopamine neuroactivity within the striatum, coincident with loss of dopamine-secreting (dopaminergic) neurons and DaT. The PS diseases predominantly consist of multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and Parkinson's Disease. These conditions are, among other features, characterized by tremor. In contrast, the form of tremor identified as "Essential tremor" (ET) is not thought to be associated with loss of dopaminergic neurons and DaT. Hence, a reliable imaging test for DaT could assist the clinician in distinguishing PS from ET.

The DaTscan clinical program verified the usefulness of the test in distinguishing PS from ET based upon a single study (Study 304) that compared baseline DaTscan images to clinical diagnoses after three years of follow-up. This duration of follow-up was regarded as a reliable clinical diagnostic standard, particularly since it was formed by movement disorder specialists. A supportive study (Study 003) provided additional data describing the agreement between DaTscan images and baseline clinical diagnoses.

2. Background:

The active drug substance in DaTscan is ^{123}I-ioflupane, a cocaine derivative with affinity for the DaT. DaT has been shown to be prevalent within the striatum, a portion of the brain that consists of two major parts within each cerebral hemisphere, the caudate and putamen. The presence of DaT on the surface of dopaminergic neurons assists in the

recycling (uptake) of dopamine back into the neurons. Exploiting the DaT affinity of ^{123}I-ioflupane, the applicant proposed that injection of ^{123}I-ioflupane (DaTscan) into humans allowed visualization of the striatum on SPECT imaging and implicitly, the detection of abnormal distribution of DaT and/or dopaminergic neurons throughout the striatum.

Diagnostic radiopharmaceuticals (such as DaTscan) have specific regulations pertaining to their demonstration of safety and effectiveness (21 CFR 315). The regulations note that the effectiveness of a diagnostic radiopharmaceutical is assessed by evaluating its ability to provide useful clinical information related to its proposed indication. The regulations provide a list of potential indication categories and the efficacy expectations for each category. For example, to obtain a "biochemical" type of indication (as the applicant generally proposed for DaTscan), the regulations note that, "The claim...is established by demonstrating in a defined clinical setting, reliable measurement" of the biochemical process. The regulations also note that the usefulness of the diagnostic information is determined by comparison with a reliable assessment of actual clinical status which may be provided by: (a) a diagnostic standard, (b) standards of demonstrated accuracy or (3) "established in another manner, e.g., patient follow-up." The DaTscan clinical program generally addressed a "biochemical" type of indication in which these regulatory expectations were addressed in the following manner (Table 1):

Table 1. Regulatory Characterization of DaTscan

Clinical Usefulness	• Study 304 used clinical follow-up as a comparator for DaTscan images; Follow-up extended over a 3 year period • Study 003 was a supportive study that compared DaTscan images to baseline clinical diagnoses
Reliability	• Data verified specificity of ioflupane binding to the human DaT (autoradiography of human brain slices with specific competition analyses) and *in vitro* binding assays of ioflupane to recombinant DaT • Study 304 also was a "defined clinical setting" that allowed a reliable estimate of agreement between DaTscan images and clinical diagnoses • Animal studies verified binding of radiolabeled ioflupane to striatum with displacement by DaT competitors

3. Chemistry, Manufacturing and Controls:

The original cycle Chemistry review was performed mainly by Dr. Ravindra Kasliwal. The microbiology review was performed by Dr. Bryan Riley. The reviewers verified acceptable manufacturing procedures and facility inspections also supported the approval of the application.

4. Nonclinical Pharmacology/Toxicology:

I concur with the original cycle conclusions reached by the Dr. Sunday Awe, the pharmacology/toxicology reviewer who noted that there are no outstanding pharm/tox issues that preclude approval. The pharmacology/toxicology provided some labeling recommendations which were incorporated into draft labeling. No post-marketing commitments were requested. The animal data were particularly robust in demonstrating that ioflupane binds specifically to the DaT within the striatum of animals. Autoradiography of human brain slices verified the specificity of ioflupane for DaT within the human brain.

5. Clinical Pharmacology/Biopharmaceutics:

I concur with the conclusions reached by the original cycle clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. The reviewer provided some recommendations for labeling which were incorporated into the draft labeling text. No outstanding issues were identified and no post-marketing commitments were requested.

The reviewer provided specific recommendations for certain pharmacology information within the labeling and these items were incorporated into the final labeling.

6. Clinical Microbiology:

The original cycle microbiology reviewer recommended approval and I concur with his findings.

7. Clinical/Statistical-Efficacy:

Dr. Phillip Davis provided the main clinical review and Dr. Mark Levenson provided the main statistical review and below I summarize the major clinical data.

Overall, three major clinical confirmatory clinical studies were submitted in the application, Studies 003, 304 and 301. Study 301 examined image results among patients with dementia while the other two studies examined patients with tremor. A supportive study (the Walker Study) was also supplied; this study compared DaTscan images to autopsy diagnoses of dementia. Hence, the development program focused upon two major areas: dementia and clinically uncertain PS.

The basis for potential use of DaTscan in PS was described in the introduction to this document. The basis for the potential use of DaTscan in dementia relates to the observation that Dementia with Lewy Bodies (a specific type of dementia) has been associated with loss of DaT while other types of dementia (e.g., Alzheimer's) generally are not associated with DaT loss.

a. Evaluation of patients with tremor:

The safety and efficacy of DaTscan were evaluated in two multicenter, single-arm studies (Study 304 and Study 003) that evaluated 287 adult patients with tremor. In the studies, DaTscan image outcomes were compared to a clinical diagnostic standard of "PS" or "non-PS". The clinical diagnostic standard for "PS" consisted of the following diagnoses: Parkinson's disease, multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). These three conditions have been associated with dopaminergic neurodegeneration and DaTscan imaging was not designed to distinguish among the conditions. The reference clinical diagnostic standard for "non-PS" consisted of an essential tremor (ET) diagnosis or other non-PS diagnosis. Both studies excluded subjects with concomitant medications known or suspected of interacting with striatal uptake of DaTscan. Three to 6 hours after DaTscan administration, subjects underwent SPECT imaging with a variety of multi-headed cameras or a multi-detector single-slice systems.

DaTscan images were evaluated by readers blinded to clinical information. Study 304 readers had no other role in patient assessment; Study 003 readers included site investigators. The clinical diagnostic standards were the clinical diagnoses established by a consensus panel of movement disorder specialists that evaluated data inclusive through 36 months of follow-up (Study 304) or the investigator-determined baseline clinical diagnosis (Study 003). Study 304 consisted of patients with early features of Parkinsonism; patients with features suggestive of MSA or PSP were excluded. Study 003 consisted of patients with clinically established diagnosis of PS (Parkinson's disease, MSA, PSP) or ET.

Table 2 shows the positive percent agreement and negative percent agreement of the DaTscan image results with the reference clinical diagnostic standard. Positive percent agreement represents the percent of patients with abnormal DaTscan images among all the patients with a clinical diagnostic reference standard of PS. The negative percent agreement represents the percent of patients with normal DaTscan images among the patients with a non-PS clinical diagnostic reference standard.

Table 2. Positive and Negative Percent Agreements for Studies 304 and 003

Reader	Positive percent agreement (95 % CI) (% patients with an abnormal DaTscan image among patients with PS)	Negative percent agreement (95 % CI) (% patients with a normal DaTscan image among patients with non-PS)
Study 304 (patients with early signs and/or symptoms of PS)		
Reader A, n = 102	78 (66, 87)	97 (83, 100)
Reader B, n = 99	78 (66, 87)	97 (83, 100)
Reader C, n = 101	79 (67, 88)	97 (83, 100)
Study 003 (patients with established diagnoses of PS or ET)		
Reader A, n = 185	93 (88, 97)	96 (81, 100)
Reader B, n = 185	97 (93, 99)	74 (54, 89)
Reader C, n = 185	96 (92, 99)	85 (66, 96)
Reader D, n = 185	92 (87, 96)	93 (76, 99)
Reader E, n = 185	94 (90, 97)	93 (76, 99)

b. Evaluation of patients with dementia:

Study 301 evaluated patients with various forms of dementia. The study compared DaTscan images to baseline clinical diagnoses, as well as clinical diagnoses after one year of follow-up. (b) (4)

The "Walker" study compared dementia diagnoses from autopsy histopathology to DaTscan images made many months prior to death. Within the "Walker" Study, clinical diagnoses were incorrect in 9/22 patients and DaTscan findings were incorrect in 4/22 patients. The small sample sizes as well as limitations within the histopathology diagnostic criteria were regarded by the FDA review team as important limitations to these data.

(b) (4)

8. Safety:

The most notable safety findings pertain to the non-USA post-marketing experience. DaTscan has been marketed in Europe since 2000. During this time hypersensitivity reactions have uncommonly been reported. These reactions generally consisted of rash and pruritus and either resolved spontaneously or following the administration of

corticosteroids and anti-histamines. The risk for hypersensitivity reactions was cited as a warning in the label. No serious adverse reactions were observed in the clinical trials and adverse reactions were uncommon (<1% of patients). Adverse reactions consisted of headache, nausea, vertigo, dry mouth or dizziness. These reactions were of mild to moderate severity.

The risk for thyroid uptake of radioactive iodine was highlighted as a warning within the DaTscan label and the label includes direction for administration of a thyroid uptake blocking agent to prevent thyroid accumulation of radioactive iodine.

The review team regarded labeling as a sufficient measure for risk management. No risk evaluation and mitigation strategy was regarded as necessary, a conclusion supported by the OSE/DRISK review.

Post-marketing Requirements (PMR): none

Post-marketing Commitments: a survey-type study to estimate DaTscan performance in non-Caucasians as compared to Caucasians.

9. Advisory Committee Meeting:

This application was presented to the Peripheral and Central Nervous System Advisory Committee on August 11, 2009. The committee voted (11 to 2) to conclude that the presented data represented a favorable risk to benefit profile for DaTscan.

10. Pediatrics:

Clinically uncertain PS was regarded as not applicable to the pediatric patient population and pediatric studies were waived.

11. Other Relevant Regulatory Issues:

Overall, the supplied data supports a favorable risk-benefit finding for the drug. The drug was associated with relatively few safety concerns and no unique risk management activities were regarded as necessary. In other matters, the FDA inspection of clinical sites disclosed no remarkable findings; financial disclosure expectations have been met.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RAFEL D RIEVES
01/05/2011

F

Department of Health

MEDICINES CONTROL AGENCY

Market Towers 1 Nine Elms Lane London SW8 5NQ

Telephone 0171-273 -0327
Facsimile 0171-273 -0443

Room 1418

Dr Smith
Amersham International PLC
Amersham Laboratories
White Lion Rd.
Amersham
Bucks HP7 9LL

Our Ref 00221/0134/A 47178
Your Ref

19 June 1997

Dear Dr Smith

THE MEDICINES (EXEMPTION FROM LICENCES)(CLINICAL TRIALS) ORDER 1995 (S.I. 1995/2808)
THE MEDICINES (EXEMPTION FROM LICENCES AND CERTIFICATES) (CLINICAL TRIALS) ORDER 1995 (S.I. 1995/2809)
PRODUCT: FP-CIT INJECTION

I am writing to confirm that the Licensing Authority raises no objection to your carrying out a clinical trial in accordance with your notification dated 14 May 1997. You may therefore carry out the trial as notified, but I must remind you of the conditions set out in my letter of 16 May 1997 to which you should now attach this confirmation of exemption.

Remarks:
* It is assumed that all women of childbearing potential will be tested for pregnancy and excluded if the test is positive.
* For any extensions to this clinical trial a fuller discussion of any undesirable pharmacological effects in man should be provided. If this information is not available from clinical studies, data from animals should be provided, especially for effects on the cardiovascular and respiratory systems.
* A reference to the literature for the synthesis of the key starting material, N-omega-fluoropropyl-2beta-carbomethoxy-3beta- (4-trimethylstannylphenyl)-nortropane is not an acceptable method of providing information on this compound. Before your trials can begin, data are required on the synthesis as employed by you to demonstrate that the correct molecule of an appropriate standard is produced.

In accordance with Article 5(1) of S.I. 1995/2808, this exemption is effective from 19 June 1997 and will continue for a period of three years unless terminated in accordance with the conditions referred to above.

Yours sincerely

Mrs. S. Syed

Amersham International plc
Amersham Laboratories
White Lion Road
Amersham
Buckinghamshire
England HP7 9LL

Tel: 01494 544000
Fax: 01494 543588

Amersham HEALTHCARE

CTX Section
Medicines Control Agency
Market Towers
1 Nine Elms Lane
London SW8 5NQ

voice mail & direct tel: 01494 54 3362
direct fax: 01494 54 3821

27 June 1997

Dear Sirs,

CTX 00221/0134/A

Thank you for your letter of 19 June 1997 confirming that the Licensing Authority has granted an exemption from licences and certificates for the above trial with effect from 19 June 1997.

We note your request that all women of childbearing potential will be tested for pregnancy and excluded if the test is positive, and we confirm that these requirements will be incorporated into the trial protocol.

We also note your comment that additional information on pharmacological effects should be provided should the trial be extended.

In your letter you remark that data are required to demonstrate that the key starting material N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-trimethylstannyphenyl)nortropane is synthesised in such a fashion which demonstrates that the correct molecule of an appropriate standard is produced. Please find enclosed additional data to provide further assurance of the quality and identity of this material.

The compound in question is not synthesised directly by us, but is manufactured under contract by Research Biochemicals International for Cygne BV. Detailed information characterising this key starting material is enclosed in compliance with your letter of 19 June and we look forward to receiving confirmation that these data now meet with your approval and that the clinical study can begin.

Yours faithfully,

[illegible]

[illegible] Smith
Group Regulatory Affairs
Amersham Healthcare R & D

Department of Health
MEDICINES CONTROL AGENCY
Market Towers 1 Nine Elms Lane London SW8 5NQ
Telephone 0171 273 -0327
Facsimile 0171 273 -0443
Room 1418
Dr Smith
Amersham International PLC
Amersham Laboratories
White Lion Rd
Amersham
Bucks HP7 9LL

Our Ref 0022/0134/A 59158
Your Ref

23 July 1997

Dear Dr Smith

THE MEDICINES (EXEMPTION FROM LICENCES)(CLINICAL TRIALS) ORDER 1995 (S.I. 1995/3805)
THE MEDICINES (EXEMPTION FROM LICENCES AND CERTIFICATES) (CLINICAL TRIALS) ORDER 1995 (S.I. 1995/2809)
PRODUCT: FB-CIT INJECTION
PROTOCOL:

Following our telephone conversation of 23 July 1997, the logic of the presentation in your letter of 27 June 1997 is now clear and trials may begin.

Yours sincerely

Miss O Arnold

6

Clinical Study Report
DP008-003

GE Healthcare

Title: A MULTICENTRE, PHASE III, CLINICAL STUDY TO COMPARE THE STRIATAL UPTAKE OF AN INTRAVENOUS SOLUTION CONTAINING A DOPAMINE TRANSPORTER RADIO-LIGAND, [123I]FP-CIT, IN PATIENTS DIAGNOSED WITH PARKINSON'S DISEASE, MSA, PSP AND DEFINITE ET (US VERSION)

Authorization:

Name	Capacity	Date
Horgan Kevin	Global Head Clinical	17-12-2008 15:45:18

US Version

GE Healthcare Ltd. and its Affiliates (hereinafter referred to as the "sponsor")

Clinical Project Leader
Paul Sherwin, MD
101 Carnegie Center
Princeton
NJ 08540
USA
Tel: +1 (609) 514 6820
Fax: +1 (609) 514 6855

Study Initiation Date: 25 August 1997
Study Completion Date: 24 February 1998

This study was conducted in compliance with Good Clinical Practices, according to the ICH Harmonised Tripartite Guideline.

Confidentiality Statement

2 SYNOPSIS

Name of Sponsor/Company: GE Healthcare Ltd. and its Affiliates	**Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented:**	**(For National Authority Use only)**
Name of Finished Product: DaTSCAN™		
Name of Active Ingredient: [^{123}I]Ioflupane (Ioflupane)	**Volume:**	
	Reference:	

Title of Study: A Multicenter, Phase III, Clinical Study to Compare the Striatal Uptake of an Intravenous Solution Containing a Dopamine Transporter Radio-ligand, [^{123}I]FP-CIT, in Patients Diagnosed with Parkinson's Disease, Multiple System Atrophy, Progressive Supranuclear Palsy and Definite Essential Tremor (US Version).

Investigators and Study Centers: Six centers in Europe participated in the study.

Investigators and Centers for Independent Evaluation of Images: Five of the study investigators were chosen to perform a Blinded Read (blinded image evaluation [BIE]) of the images obtained from all study subjects.

Publication (reference): None

Study Period: 25 August 1997 to 24 February 1998. | **Phase of Development:** 3

Objectives:

This study report is a US version prepared from the original European clinical study report (CSR). The reasons for preparing a US version were:

(1) Conversion of the CRF data to CDISC SDTM format and the analysis data to '99 compliant format.
(2) Focus on key endpoints of clinical relevance.
(3) To present data in accordance with FDA guidance.

Primary:

The original primary objective was to determine the sensitivity and specificity of striatal uptake of DaTSCAN™ in patients with Parkinsonian syndrome (PS) involving striatal dopaminergic deficit (SDD) (specifically Parkinson's disease [PD], multiple system atrophy [MSA] or progressive supranuclear palsy [PSP]) compared with uptake in patients with essential tremor (ET; no SDD). The revised objectives for the US report are presented below.

Secondary:

(1) To assess safety parameters (hematology, biochemistry and urinalysis, vital signs and electrocardiogram [ECG]), and the adverse event (AE) profile in patients/volunteers following a single i.v. injection of DaTSCAN™.
(2) To assess the striatal uptake of DaTSCAN™ in healthy volunteers (no SDD) as a means to facilitate the calibration of imaging equipment at each study site.

Study Design: This was a multicenter, comparator-group, open, non-controlled, non-randomized clinical study to compare the striatal uptake of DaTSCAN™ in patients with PS (SDD; specifically, patients with PD [SDD], MSA [SDD] or PSP[SDD]) to the uptake in patients diagnosed with ET (no SDD).

Selection of Subjects:

Main Inclusion Criteria (Including Diagnosis):

(1) Male and female non-patient volunteers aged 50 to 80 years with a good age-appropriate health as established by clinical examination during screening.
(2) Male and female patients aged 40 to 80 years with documentation of a clinical diagnosis of either:
- PD (SDD), MSA (SDD), or PSP (SDD), and satisfaction of the UK Parkinson's Disease Society (UKPDS) Brain Bank criteria step 1, or
- ET (no SDD) and satisfaction of the Findley & Koller definite ET (no SDD) definitions and behavioral classifications for clinical diagnosis.

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Name of Active Ingredient: [^{123}I]Ioflupane (Ioflupane)	**Volume:**	
	Reference:	

Number of Subjects:
All subjects recruited into the study with an available DaTSCAN™ image were included in the intention-to-diagnose (ITD) population for the evaluation of efficacy. This population included withdrawn patients who had a DaTSCAN™ image. All subjects enrolled with an available DaTSCAN™ image who did not violate the protocol in any way were included in the per-protocol (PP) population for the evaluation of efficacy.

Planned: 186 evaluable subjects (148 patients and 36 healthy volunteers)
Enrolled: 248
Received study drug: 224
Evaluable for safety: 224
Evaluable for efficacy (intent to diagnose [ITD] population): 220
Evaluable for efficacy (per-protocol [PP] population): 157

Treatment of Subjects:
Investigational Medicinal Product: DaTSCAN™, a single i.v. injection containing 111 to 185 MBq (3 to 5 mCi).
Comparator: Not used.
Standard of Truth: The clinical diagnoses of PD (SDD), MSA (SDD), PSP and ET (no SDD) made by the on-site clinical investigator using robust standardized diagnostic criteria served as the standard of truth (SOT).
Duration of Treatment: 1 day

Changes to the Statistical Analysis Plan for the US revision of the Clinical Study Report
Endpoints:
Primary Efficacy Variable(s): The revised primary endpoint of the study was the sensitivity and specificity of the on-site institutional read of single-photon emission computed tomography (SPECT) images in differentiating between PS (SDD) and non-PS (no SDD) subjects (through the detection of SDD) using the clinical diagnosis as the SOT. The exact 95% confidence interval (CI) was calculated for both the sensitivity and specificity. All statistical tests were two-sided and presented at a 5% level of significance.
Secondary Efficacy Variable(s): In the Blinded Read, images were interpreted as in the institutional read. Each blinded reader's assessments were included in 1 overall summary. A "consensus" (majority) blinded read assessment was defined as agreement of a majority (3 or more) of the 5 blinded readers. The "consensus" (majority) assessment was analyzed as described for the primary variable. Only subjects with "consensus" (majority) assessments were included in this analysis. The sensitivity ("response rate" in the PS population; equal to the number of abnormal reads divided by the total number of reads) for the institutional read and for the "consensus" blinded read assessments was calculated along with the 95% CI. Analyses were also conducted to detect any variation of sensitivity with change in Hoehn and Yahr (H&Y) or Unified Parkinson's Disease Rating Scale (UPDRS) score category (using a UPDRS score of 22 as the threshold). Specificity ("response rate" in the non-PS population, equal to the number of normal reads divided by the total number of reads) was also determined for the institutional and Blinded reads.
Inter-reader Agreement (On-Site and "Consensus" [Majority] BIE Reads): Agreement between each pair of readers with respect to the SPECT visual assessment findings (abnormal/normal) was assessed using κ statistics. Cohen's κ coefficient of agreement between the readers was estimated with 95% CIs. Since its calculation used an approximation (based on the normal distribution), although the maximum value for the κ coefficient was 1, it was possible for the upper limit of these CIs to exceed 1. In these cases, κ values >1 were to be interpreted as 1 (i.e., perfect agreement). Kappa was ≤0 when the observed agreement is less than or equal to chance and it equals 1 when there was perfect agreement. The stronger the agreement the higher was the κ value.
The original European clinical study report (CSR) included additional endpoints for on-site and BIE reads by

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center and by age and semi-quantitative results. These data were not re-analyzed for this US report, but the original results are summarized with reference to the section of the European CSR where full details can be found.

Endpoints:

Primary Efficacy Endpoint: The co-primary endpoints of the study were the sensitivity and specificity of the on-site institutional read of SPECT images in detecting or excluding SDD.

Secondary Efficacy Endpoints:

(1) Visual assessment of DaTSCAN™ striatal uptake from SPECT images as determined by the Blinded Read (BIE) diagnosis of a panel of readers, blinded to the clinical diagnosis, which was derived from the patients' visual image alone). Sensitivity was determined for subjects in each Hoehn & Yahr (H&Y) grade and for subjects in each of 2 UPDRS categories (<22 or ≥22). Since H&Y scores were collected only for subjects with PS, specificity was not analyzed by H&Y score.

(2) Inter-reader agreement as determined from the five BIE readers and on-site reads with respect to the DaTSCAN™ SPECT visual assessment findings (abnormal/normal) and assessed using Cohn's kappa (κ) statistics.

Also analyzed was the semi-quantitative assessment of regions of interest (original European CSR only).

Safety:

AE, laboratory, ECG, vital signs, medical history and concomitant medication data were used in the evaluation of the safety profile of DaTSCAN™.

Statistical Analyses:

The primary and secondary analyses were performed on both the PP (evaluable) and intent to diagnose (ITD) efficacy populations. All response rates used a one sided 95% CI. All p-values presented were two-sided and set at a 5% level of significance. Differences in the binary response rates of abnormal/normal striatal uptake were analyzed using Fisher's exact test where appropriate. Descriptive summaries of baseline data were produced. There was no formal analysis of safety data planned or conducted for this study. Relevant datasets were summarized and tabulated.

Summary of Results:

Efficacy:

Based on the visual assessment of striatal uptake pattern as determined by institutional readers, the sensitivity and specificity of DaTSCAN™ SPECT in detecting or excluding a SDD were 97.5% and 98.4%, respectively. PP results were similar. The "consensus" (majority) BIE assessments gave very similar results for ITD analyses with sensitivity of 94.9% and specificity of 93.5%. PP results were also similar.

By BIE reader, sensitivity and specificity were consistent in both the ITD and PP populations. In the ITD population, sensitivity among the readers ranged from 92.4% to 96.8% and specificity ranged from 80.6% to 96.8%.

Inter-reader agreement between the 5 BIE readers was excellent, with Cohen's κ values ranging from 0.83 to 0.92; the pooled coefficient for all 5 readers was 0.87. Agreement between the BIE readers compared with the on-site readers showed that the on-site reader agreement was similar, with Cohen's κ values ranging from 0.88 to 0.94.

Sensitivity did not vary by H&Y score in the ITD population for onsite DaTSCAN™ SPECT or "consensus" (majority) BIE assessments ($p>0.999$ and $p=0.869$, respectively). Sensitivity by H&Y disease stage ranged from 96.7% to 100.0% for on-site read and 94.3% to 100.0% for the BIE read. Results were similar for the PP population.

Similarly, sensitivity did not vary by UPDRS score in the ITD population similarly showed no evidence of a significant difference in sensitivity for onsite DaTSCAN™ SPECT or "consensus" (majority) BIE assessments ($p>0.999$ and $p=0.869$, respectively). Sensitivity by UPDRS screening scores (<22 or ≥22) were 98.6% and

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	Reference:	

97.1%, respectively, for on-site read and 97.1% and 95.6%, respectively, for BIE read. Results were also similar for the PP population.

The results of the on-site and "consensus" (majority) BIE SPECT assessments compared with the clinical diagnosis for the ITD population analyses showed that the visual assessment of DaTSCAN™ images had high sensitivity and specificity for detecting or excluding a SDD in patients with movement disorders.

Safety:

Among the 224 subjects in the safety population, 36 subjects (16%) experienced a total of 69 AEs and only 2 AEs were severe: PD exacerbation (1 subject) and headache (1 subject). Fifteen subjects (7%) experienced 32 AEs that were considered related to DaTSCAN™; the most common related AEs were headache (7 subjects) and vertigo, hunger, and formication (paresthesia) (3 subjects each). One serious adverse event (SAE) of PD exacerbation was reported but was not deemed to be related to DaTSCAN™.

No safety concerns were noted in the results for clinical laboratory tests, vital signs, or ECG. These study results indicate DaTSCAN™ to be a safe and well-tolerated radiopharmaceutical.

Conclusions:

Visual inspection of DaTSCAN™ images has high sensitivity and specificity for detecting or excluding a SDD in patients with movement disorders. The inter-reader agreement is excellent. DaTSCAN™ has an excellent safety profile.

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3.1 Overall Report Table of Contents

3.2 List of Tables

3.3 List of Figures

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
[^{123}I]FP-CIT	[^{123}I] N-ω-fluropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane
AE	Adverse Event
ANOVA	Analysis of variance
BIE	Blinded image evaluation
CI	Confidence interval
CL	Confidence level
CRF	Case Report Form
CRO	Contract research organization
CSR	Clinical study report
DaT	Dopamine transporter
DaTSCAN™	[^{123}I] N-ω-fluropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane, [^{123}I] FP-CIT, or [^{123}I] ioflupane
DLB	Dementia with Lewy bodies
ECG	Electrocardiogram
ET	Essential tremor
F1	Follow-up visit
GGT	Gamma glutamyl transferase
GCP	Good Clinical Practice
H&Y	Hoehn & Yahr
i.v.	Intravenous
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
ITD	Intent to diagnose
^{123}I	Iodine-123
MSA	Multiple system atrophy
NINDS-SPSP	National Institute for Neurological Disorders and the Society for Progressive Supranuclear Palsy
NPV	Negative predictive value
PD	Parkinson's disease
PP	Per-protocol
PPV	Positive predictive value
PS	Parkinsonian syndrome; a group term for patients diagnosed with PD, MSA or progressive supranuclear palsy
PSP	Progressive supranuclear palsy
ROI	Region of interest
S1	Pre-imaging screening visit
S2	Additional screening visit
SDD	Striatal dopaminergic deficits
SAE	Serious adverse event
SPECT	Single-Photon Emission Computerized Tomography

Abbreviation	Definition
SOC	System organ class
SOP	Standard operating procedure
SOT	Standard of truth
UK	United Kingdom
UKPDS	UK Parkinson's Disease Society
UPDRS	Unified Parkinson's Disease Rating Scale
WHO	World Health Organization

5 ETHICS

5.1 Independent Ethics Committee or Institutional Review Board

Before the study was initiated at each site, the protocol was submitted to and approved by, or received a favorable opinion from, an Independent Ethics Committee (IEC) according to national or local regulations. Any protocol amendments were also submitted for relevant approval. A list of all IECs consulted and the name of each committee's chair is appended in Section [16.1.3].

5.2 Ethical Conduct of the Study

This study was conducted in full accordance with the 1996 revision of the Declaration of Helsinki, the *Good Clinical Practice: Consolidated Guideline* adopted by the International Conference on Harmonization (ICH), and any applicable national and local laws and regulations.

The investigators were responsible for performing the study in accordance with the protocol and ICH E6-Good Clinical Practice (GCP), for collecting, recording, and reporting the data accurately and properly. Agreement of the investigator to conduct and administer this study in accordance with the protocol was documented in separate study agreements with the sponsor and other forms as required by national authorities in the country where the study site was located.

The principal investigator was responsible for the conduct and administration of the study at that site, and for contacts with study site management, the IEC, and with local non-regulatory bodies.

5.3 Subject Information and Informed Consent

Written and oral information about the study in a language understandable to the subject was given to all subjects and their caregivers or informants. The information provided an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force.

Written informed consent was obtained from each subject and his or her caregiver or informant before any study procedures or assessments were done and after the aims, methods, anticipated benefits, and potential hazards were explained. It was explained to the subjects and their caregivers or informants that they were free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

The subject's willingness to participate in the study was documented in writing in a consent form that was signed by the subject and his or her caregiver or informant with the date and time

of signature indicated. The investigators kept the original consent forms and copies were given to the subjects.

A sample informed consent form and any other written information provided to the subject and their caregiver or informant are appended in Section [16.1.3].

The subject's willingness to participate in the study was documented in writing in a consent form. This occurred at all sites with the following exceptions. At study site 004 in Amsterdam, Subject 70 used a 'stamp' instead of his signature as he could not write due to Parkinson's disease (PD). At study site 006, consent for Subject 257 was obtained by a witness, but it was not clear whether the witness was a legally acceptable representative of the subject. Due to a misunderstanding at study site 002 in Ulm, informed consent dates were not personally recorded by the subjects or by the investigator or the investigator's appointed delegate. Dates were personally recorded by some of the subjects at study site 004 and at study site 006. Dates were personally recorded by the subjects, or where applicable their legally acceptable representative, and by the investigators or the investigator's appointed delegate at the remaining study sites.

5.4 Authority Approval

Clinical study clearance from the relevant regulatory/health authorities was obtained in all countries before the start of the study. For sites in Germany and the United Kingdom (UK), the sponsor and the investigators agreed not to recruit any subjects into the study before receiving a favorable opinion from the applicable radiation safety board or isotope committee.

Country	Radiation Safety Board/Isotope Committee
Germany	Bundesamt für Strahlenshutz (BfS)
UK	Administration of Radioactive Substances Advisory Committee (ARSAC), Department of Health

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The sponsor was responsible for medical overview, overall clinical coordination, partial clinical data monitoring, and regulatory aspects of the study. All data management were conducted by BIOS International Ltd., a contract research organization (CRO) based in the UK. Statistical analyses in this report were conducted by i3 Statprobe, a CRO based in the United States. The investigational medicinal product (IMP, DaTSCAN™ Injection [DaTSCAN™]) was supplied by Cygne, a subsidiary of the sponsor located in The Netherlands to the principal investigator at each site (Table 1).

Six European study sites were initiated. Together, the 6 sites assigned 250 study numbers to 248 subjects (two subjects were re-screened and assigned new study numbers); 224 were dosed with DaTSCAN™. Table 1 provides a list of principal investigators, site locations, and the number of subjects enrolled and the number administered DaTSCAN™ at each site.

Table 1 List of Investigators and Study Enrollment

Study Center No.	Principal Investigator	Center Location	Number of Subjects Enrolled[a] / Given DaTSCAN™
001	Professor W.H. Oertel Professor K. Joseph	Philipps University Hospital, Marburg, Germany	36/33
002	Professor K. Tatsch Dr. J. Schwarz	Ludwig Maximilians University Hospital, Munich, Germany Neurologisch Klinik der Universitat, Ulm, Germany	41[a]/37
003	Dr. D. Grosset Dr. J. Patterson	Southern General Hospital, Glasgow, UK	84/70[b]
004	Dr. J. D. Speelman Dr. M.W.I.M. Horstink	Amsterdam Medical Center, Amsterdam, The Netherlands University Hospital, Nijmegen, The Netherlands	36/34
005	Dr. A.J. Lees Dr. D.C. Costa	Middlesex and National Hospitals, London, UK	33/31
006	Professor R. Dierckx Dr. D. Decoo	University Hospital Gent, Belgium Elisabeth Hospital, Bruges, Belgium	20[a]/12[c]

[a] 250 study numbers were assigned to 248 subjects; 2 subjects (nos. 155 and 158) were re-screened and given new subject numbers (187 and 254, respectively).
[b] 71 subjects were reported as receiving a DaTSCAN™ dose; however, this count included 1 healthy volunteer who attended the imaging visit but withdrew prior to receiving DaTSCAN™ (Listing [15.2.1] in EU CSR).
[c] 7 Parkinsonian Syndrome subjects were not listed in Listing [15.2.1] in the EU CSR, but were listed in Listing [15.1.7] in the EU CSR and had received DaTSCAN™.
REF: Listings [15.1.7] and [15.2.1] in the EU CSR.

A list of investigators and other important study personnel, including documentation of each investigator's qualifications, is appended in Section [16.1.4].

For all laboratory parameters, with the exception of prothrombin time, 1 central laboratory, MediLab, was used for UK sites, (London and Glasgow), and a second, Spranger & Kloss, for the central European sites (Munich/Ulm, Marburg, Amsterdam and Gent/Brugge). These central laboratories used comparable, standardized methods for the assessment of hematology, biochemistry and urinalysis parameters.

All prothrombin time assessments for all patients/volunteers were conducted at the end of the study by MediLab.

7 INTRODUCTION

Assessment of patients with symptoms and signs of movement disorders and dementia remains a formidable challenge, despite advances in knowledge of the pathophysiology of these conditions. One new approach is based on research showing that some of these disorders have in common the progressive, irreversible loss of a specific type of neuron, namely the dopaminergic nigrostriatal neuron. This type of neuron is found in the basal ganglia, which are nuclei (groups of neurons) in the brain that modulate both movement and cognition; consequently, conditions that affect the basal ganglia may result in movement disorders and/or dementia [Cote and Crutcher 1991; Martin 1996].

One especially key part of the basal ganglia is the substantia nigra pars compacta, a nucleus that contains pigmented dopaminergic neurons that project to, and synapse with, neurons in another nucleus called the striatum; these neurons are known collectively as the nigrostriatal pathway. They are referred to as dopaminergic because dopamine is the neurotransmitter that passes signals between neurons. Each of the two striata (left and right) is composed of two smaller regions called the caudate and putamen. The striata are depicted in Figure 1 (in green) as comma-shaped structures; the caudate nuclei form the "heads" of the "commas" and the putamen nuclei form most of the "tails".

Figure 1 3-Dimensional Diagram of Human Brain Showing the Striata (in Green) as Two Comma-Shaped Structures

Source: http://www.nimh.nih.gov/images/news-items/striatumcortex1.jpg

Dopaminergic nigrostriatal neurons bear a protein, the dopamine transporter (DaT) protein, which functions to terminate inter-neuronal signaling by removing dopamine from the synapse. Dopamine re-uptake is achieved by high affinity binding to the DaT. In addition to binding dopamine tightly, the DaT protein also binds cocaine (a dopamine re-uptake inhibitor) and cocaine analogs with high affinity. Radiolabelled cocaine analogs have been developed for imaging of the dopaminergic nigrostriatal neurons where they synapse in the striata.

One such analog is DaTSCAN™ [Ioflupane (^{123}I) Injection], a radiopharmaceutical product that was developed for assessing the integrity of dopaminergic nigrostriatal neurons. The active substance in DaTSCAN™, [^{123}I]ioflupane, binds reversibly with high affinity to the DaT protein, thereby making it a specific marker for dopaminergic nigrostriatal neurons. The radioactive decay of the iodine-123 releases gamma radiation which allows visualization of the striata through single-photon emission computed tomography (SPECT) imaging. Because DaTSCAN™ occupies less than 1% of DaT protein binding sites, there are no cocaine-like pharmacologic effects (about 60% occupancy is needed for cocaine-like effects).

Following intravenous (i.v.) injection (111 to 185 MBq, or 3 to 5 mCi) of DaTSCAN™, [^{123}I]ioflupane is distributed rapidly to the striata, reaching stable activity levels within approximately 3 hours which provides a stable imaging window of approximately 3 to 6 hours. DaTSCAN™ images depict normal striata (Figure 2) as symmetric comma or crescent shaped areas of increased activity (increased brightness). Abnormal striata lack activity in some regions and thus appear as incomplete structures (Figure 3). In the most severe cases of neuronal loss, striatal activity may be completely absent. These characteristic image patterns allow the facile determination of a patient's striatal dopaminergic status. In PD patients, autopsy studies have consistently revealed that approximately 60% of dopaminergic nigrostriatal neurons must be lost before the onset of symptoms; because the loss is so extensive, it is readily apparent in DaTSCAN™ images of patients with symptoms and signs of movement disorders. Thus, quantification of the image data is not needed to differentiate normal from abnormal striatal images.

Figure 2 DaTSCAN™ ([^{123}I]Ioflupane) SPECT image in a healthy subject showing striata as bright "comma"-shaped regions

Figure 3 DaTSCAN™ ([^{123}I]ioflupane) images showing areas of reduced striatal signal indicative of the loss of nigrostriatal neurons in a patient with early PD

Several autopsy studies have established that there is extensive loss of dopaminergic neurons in some degenerative movement disorders and dementia, such as **Parkinson's disease** (PD)

[Victor 2001; Fahn 2003; Bernheimer et al. 1973; Ma et al. 1997; Pakkenberg et al. 1991; Rinne et al. 1989; Beal et al. 1994], **multiple system atrophy** (MSA) [Wenning et al. 1997; Kume et al. 1993], **progressive supranuclear palsy** (PSP) [Hardman et al. 1997], and **dementia with Lewy bodies** (DLB) [Piggott et al. 1998], but little loss in others such as **Alzheimer's disease** (AD) [Torack and Morris 1992; Kemppainen et al. 2002], **Pick's disease** [Yokota et al. 2002], and **Huntington's disease** [Bernheimer et al. 1973].

The loss of dopaminergic nigrostriatal neurons is thus common to several neurodegenerative conditions (Parkinsonian syndromes [PS], PD, MSA, PSP, and DLB), but is not specific to any one. Accordingly, the abnormal DaTSCAN™ image patterns found in patients with conditions associated with a striatal dopaminergic deficit (SDD) are similar because the patterns are a function of uptake by the neurons, and this reduced uptake is mechanistically the same across these conditions. A DaTSCAN™ image provides visual evidence of the presence or loss of DaT function, indicating the presence or loss of dopaminergic nigrostriatal neurons.

Short of autopsy, there is no diagnostic test that can definitively diagnose the specific condition associated with the neuron loss, so current diagnosis still rests on clinical examination. However, the accuracy of clinical diagnosis is dependent upon both the duration of illness and examiner expertise. Diagnosis is easier the longer the patient has had the condition (because new symptoms may develop and the symptoms profile may better fit the typical presentation of one of the diseases in the differential diagnosis). Sub-specialists in movement disorders or dementia tend to diagnose more accurately than general neurologists, who in turn diagnose more accurately than primary care physicians. Thus, clinical diagnosis can be in error in a significant percentage of cases [Hughes et al. 1992; Walker et al. 2007], or may be delayed. Improvement in neurodiagnosis is urgently needed, and DaTSCAN™ may help fill that need. Adding knowledge of the patient's striatal dopaminergic status (as indicated by DaTSCAN™ images) to the clinical information already used in neurodiagnosis may be useful in differentiating between conditions associated with SDD and those which are not (but which may have similar clinical presentations); this differentiation may help facilitate an earlier accurate diagnosis in patients with movement disorders or dementia. Because an erroneous diagnosis may result in inappropriate therapy with possible complications [Hensman and Bain 2006; Hagenah et al. 1999], the benefits of an earlier accurate diagnosis are that the patient may receive appropriate therapy earlier, and the physician can avoid medications that are unnecessary or that may actually be detrimental (e.g., some neuroleptics have dangerous side effects in patients with DLB) [McKeith et al. 2005; Mosimann and McKeith 2003; Aarsland et al. 2005].

DaTSCAN™ was approved under a European Marketing Authorization granted in July 2000. Since that time it is estimated that approximately 168,000 patients have been administered with DaTSCAN™. In Europe, the information provided by DaTSCAN™ is used to help resolve clinically uncertain cases. A New Drug Application is being filed in the US, and the study results reported here form part of the submission.

The aim of this study was to evaluate the novel SPECT ligand, DaTSCAN™. Results of pre-clinical studies as well as Phase 1, Phase 2 and pilot clinical studies indicate that DaTSCAN™ is safe for human use, with no reports of clinically significant changes in laboratory values outside the normal range, or adverse events (AEs), following use. Visual

assessment of the SPECT images from both study groups, compared to the clinical diagnosis, was the primary efficacy end point for this study.

Although the original results of the study were reported in a European CSR, this study has been identified as principal in support of the proposed indication for the US market. Therefore, a US version of the CSR has been prepared, primarily to update the tables and figures resulting from conversion of the data to a '99-compliant format. In addition, the original European Statistical Analysis Plan has been reviewed by the sponsor and shortened by excluding those analyses considered to be redundant or non-contributory in support of the proposed indication for the US market. However, the full data set is available for review and analysis in this NDA submission.

8 STUDY OBJECTIVES

Primary

The original primary objective was to determine the sensitivity and specificity of striatal uptake of DaTSCAN™ in patients with a clinical diagnosis of PS involving SDD (specifically, PD, MSA, or PSP) compared with uptake in patients with essential tremor (ET) (no SDD). The revised primary objectives are presented in Section 9.8.9.

Secondary

(1) To assess safety parameters (hematology, biochemistry and urinalysis, vital signs and electrocardiogram [ECG]), and the AE profile in patients/volunteers following a single i.v. injection of DaTSCAN™.

(2) To assess the striatal uptake of DaTSCAN™ in healthy volunteers (no SDD) as a means to facilitate the calibration of imaging equipment at each study site.

The revised secondary objectives are presented in Section 9.8.9.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

A non-randomized, open-label, comparative study design was implemented for this phase 3, multicenter, clinical study to determine the sensitivity and specificity of striatal uptake of a single dose of DaTSCAN™ in patients with PS (disorders in which a SDD is present) compared to uptake in patients with ET (a condition commonly confused clinically with PS owing to similar symptoms, but in which no SDD is present). The dose of DaTSCAN™ selected for administration in this study has been previously shown to be safe and well tolerated. The dose formulation and selection are further discussed in Section 9.4.

The study design and procedures are illustrated in Table 2. The study consisted of at least 3 visits, including a screening visit (S1), an imaging visit, and a follow-up visit (F1). On visit S1, 250 subjects were screened to determine eligibility according to the inclusion/exclusion criteria described in Section 9.3 and, if eligible, to obtain informed consent. A second screening visit (S2) was required for some PD (SDD) patients, i.e. *de novo* patients who were required to undergo an L-DOPA challenge test, or patients for whom it was deemed inappropriate to conduct inclusion/exclusion evaluation, Unified Parkinson's Disease Rating Scale (UPDRS) assessment and Hoehn & Yahr (H&Y) 'off phase' assessments at S1.

Upon completion of visit S1, 224 eligible subjects returned to the site within a 3-week period for the imaging visit. Each subject was given a baseline evaluation and assessments as outlined in the flowchart. Thereafter, DaTSCAN™ was administered intravenously. SPECT imaging was then conducted at 3 to 6 hours post-DaTSCAN™ injection. In the period leading up to, during, and after SPECT imaging, all subjects were kept under medical supervision and any AEs observed or reported were recorded. After SPECT imaging, vital signs were taken again and subjects were released from the study site. Each subject was instructed to report at the follow-up visit any AEs experienced. Female subjects were also advised to avoid conception for a minimum of 3 complete menstrual cycles post injection.

Twenty-four to 72 hours post-imaging, subjects returned to the study site for a follow-up visit and underwent the assessments. Seven days post-injection, each subject was contacted by telephone and interviewed to determine any AEs that may have occurred subsequent to visit F1. The provision for additional follow-up visits, where/if required, was made at each study site. The need for additional visits was determined by the investigator on a case-by-case basis.

A copy of the final protocol and all 4 protocol amendments are provided in Appendix [16.1.1]. A copy of the unique pages of the case report form (CRF) is provided in Appendix [16.1.2].

Table 2 Study Flow Chart

Assessments	Screening (S1)	Screening[a] (S2)	Imaging (I)	Follow-Up (F1)	Telephone Interview
All Patients/Volunteers					
Informed Consent	X	-	-	-	-
Demographics	X	-	-	-	-
Medical History	X	-	-	-	-
Con. Med. Review	X	X	X	X	X
Vital Signs	X	-	X	X	-
ECG	X	-	-	X	-
Laboratory Work Up	X	-	X	X	-
Pregnancy Test[b]	X	-	X	X	-
Baseline Symptoms and Signs	X	-	X	-	-
Evaluation of AEs	-	-	X	X	X
Parkinsonian Patients Only					
Diagnostic and Statistical Manual of Mental Disorder Assessment (revised)	X	-	-	-	-
Parkinson's Disease Patients Only					
Challenge Test (*de novo* patients only)[c]	X[d]	X[d]	-	-	-
H&Y Assessment[e]	X[d]	X[d]	-	-	-
UPDRS Assessment	X	-	-	-	-

[a] Only required for Parkinson's disease patients where it was not appropriate to combine H&Y assessment or challenge test with other screening procedures.
[b] Females of child-bearing potential only.
[c] Only required for *de novo* Parkinson's disease patients.
[d] Could be performed either at S1 or S2 in the best interest of the patient.
[e] Must have been performed with patients in the 'off phase'.
[f] Applicable to those patients/volunteers recruited at Glasgow, Munich, Marburg & Gent only.

9.2 Discussion of Study Design

9.2.1 Justification for the efficacy analysis

This study was designed to compare the striatal uptake of DaTSCAN™ in subjects with PS (specifically, PD, MSA, or PSP — conditions known to have SDD) versus subjects with ET as well as versus healthy volunteers (neither of these groups have SDD). As already stated, ET is not associated with nigrostriatal degeneration, yet it is often confused clinically with PS because of similar symptoms. In PS, by the time symptoms have started there has been a loss of approximately 60% of dopaminergic nigrostriatal neurons [Fahn 2003]. Therefore, it is anticipated that by comparing these patient groups, a clear visual distinction can be made between the images obtained from the ET (no SDD) and PS (SDD) patient groups with respect to striatal uptake of DaTSCAN™.

The diagnostic test metrics of greatest interest to clinicians are the positive predictive value (PPV) and negative predictive value (NPV). PPV gives the probability that a patient has a disease (or abnormality) of interest given a positive diagnostic test result, and NPV gives the

probability that the patient does not have the disease or abnormality given a negative test result. However, both PPV and NPV depend on the prevalence of the disease or abnormality under consideration, so sensitivity and specificity (neither of which depend on disease/abnormality prevalence) are the preferred measures for assessing a diagnostic test. For these reasons, sensitivity and specificity (for the detection of SDD) are reported as the co-primary endpoints for this study.

The determinations of sensitivity and specificity require knowing the number of investigational test results that are true positive, true negative, false positive, and false negative. These are determined by comparing the each subject's investigational test result (in this case, the blinded visual assessment of the DaTSCAN™ images as normal [no SDD] or abnormal [SDD]) to a standard of truth (SOT). The SOT is chosen to represent the best available method of diagnosing or detecting the disease or abnormality for which the diagnostic test is being developed. In this study, the SOT for whether or not a subject had a SDD was the clinical diagnosis made at study entry using robust standardized diagnostic criteria.

9.2.2 Justification for dose and volume

An activity level of 111 MBq (3 mCi) was identified in results from a previous Phase 1 study as demonstrating a safe and well tolerated average effective dose equivalent (EDE) of 0.024 mSv/MBq, amounting to 2.66 mSv for a 111-MBq (3-mCi) injection and 4.44 mSv for a 185-MBq (5-mCi) injection. An effective dose equivalent of 5 mSv has been reported as the average effective dose equivalent per patient from nuclear medicine procedures in Europe [Beekhuis, 1988].

In order to maximize the quality of data acquired from imaging equipment of varying specifications, it was decided to validate a range of activity for the injected dose. A dose of 185 MBq (5 mCi) was considered the maximum necessary to achieve a high resolution image with a range of equipment while falling within the World Health Organization (WHO) category II limits which define acceptable exposure for patients/healthy volunteers. In addition, the recommended activity range of 111 to 185 MBq provides sufficient flexibility to allow adjustment of activity to accommodate imaging systems of varying count sensitivity.

No pharmacologic effects are expected based on the small mass dose of the active component of DaTSCAN™, [^{123}I]ioflupane, which is no more than 0.325 micrograms. This amount of material results in a DaT protein receptor occupancy of less than 1%, far below the approximately 60% receptor occupancy needed for pharmacologic effects from cocaine.

9.2.3 Justification for prohibited and permitted medication

Agents with high affinity for DaT such as amphetamine, benztropine, buproprion, cocaine, mazindol, methylphenidate, phentermine and sertraline have the potential to interfere with DaT binding of [^{123}I]ioflupane; they were therefore prohibited in the study.

In addition to the general prohibited concomitant medications listed in this section, PD (SDD) patients were required to have their anti-PD therapy withdrawn for an appropriate period of

time determined on a case by case basis prior to the H&Y assessment performed during screening (S1 or S2). Investigators were also instructed to withdraw all tremorogenic drugs to facilitate the accurate diagnosis of ET (no SDD).

Even if a medication did interact with [^{123}I]ioflupane binding, such interactions would be homogeneous throughout the striata and thus would not result in asymmetries or changes in putamen/caudate ratios. Therefore, the accuracy of visual assessment of DaTSCAN™ images as normal or abnormal should not be affected.

9.2.4 Justification for the safety plan

This study's safety monitoring plan was justifiable and adequate from a safety standpoint in view of the following:

- The design of the safety plan permitted an appropriate and adequate evaluation of the safety response to DaTSCAN™ under baseline and post-DaTSCAN™ injection conditions in the same subject.
- The measures used to assess safety were well defined and reliable within the context of the SPECT imaging environment, and the proposed safety analyses were adequate to assess the effects of DaTSCAN™.
- Prior clinical studies with DaTSCAN™ have shown that it is well tolerated without pharmacologic effects or safety concerns.
- Consistent with the low mass dose (≤ 0.325 micrograms) the [^{123}I]ioflupane occupancy of the DaT protein binding sites is less than 1%, well below the approximately 60% occupancy needed for pharmacologic effects from cocaine.

The safety plan aimed to restrict the collection of data up to and including 72 hours, based on the pharmacokinetic characteristics of DaTSCAN™ and the absence of any study procedures beyond the second follow-up phone call taking place at 1 week post administration.

9.3 Selection of Study Population

A subject was enrolled into the study only if all inclusion criteria and none of the exclusion criteria were fulfilled.

9.3.1 Inclusion criteria for healthy volunteers

Healthy volunteers (no SDD) were considered eligible for entry into the study on the basis of the following inclusion criteria:

(1) Non-patient volunteers of either sex, aged between 50 to 80 years.

(2) Volunteers with a good age-appropriate health condition as established by clinical examination during screening.

(3) In the opinion of the investigator, the volunteer understood the study information, instructions and advice, and was able and willing to comply with the protocol requirements, and visits to the study site at the required time-points. Volunteers had to be judged to be co-operative and give their written informed consent to participate in the study.

Healthy volunteers were required to conform with all of the above inclusion criteria to be considered eligible for entry into the study. The investigator was requested to achieve an even distribution of ages within the age range of 50 to 80 years, with 2 healthy volunteers per decade recruited per site.

9.3.2 Inclusion criteria for Parkinsonian syndrome patients

PS (SDD) patients were selected and screened by the investigator on the basis of the following inclusion criteria:

9.3.2.1 General Parkinsonian syndrome inclusion criteria

(1) Patients of either sex, within the age range 40 to 80 years.

(2) Documentation of a clinical diagnosis of either PD, MSA or PSP.

(3) Satisfaction of the UK Parkinson's Disease Society (UKPDS) Brain Bank criteria step 1 - Diagnosis of PS (i.e., bradykinesia with rigidity, or tremor, or both).

(4) In the opinion of the investigator, the patient understood the study information, instructions and advice, and was able and willing to comply with the protocol requirements, and visits to the study site at the required time-points. Patients had to be judged to be cooperative and give their written informed consent to participate in the study.

9.3.2.2 De novo Parkinson's disease-specific inclusion criteria

(1) For de novo patients diagnosed with PD (SDD), documented evidence of a positive challenge test to L-DOPA. A positive response was defined as an improvement equal to or greater than 30% determined using a standard tapping test, or other locally established standard method. The results, date, and dose of L-DOPA administered were recorded in the patient CRF.

9.3.2.3 Established Parkinson's disease-specific inclusion criteria

(1) For established patients diagnosed with PD who were not receiving therapy, satisfaction of the UKPDS Brain Bank criteria step 3 - Supportive Prospective Positive Criteria for PD (i.e., three or more of the following were required for diagnosis of definite PD).

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70%-100%) to L-DOPA
- Severe L-DOPA-induced chorea
- L-DOPA response for 5 years or more
- Clinical course of 10 years or more

(2) For established patients diagnosed with PD and receiving therapy, documented evidence (historical) of a positive response to therapy. A positive response in this instance was defined qualitatively as a 'good' response obtained with an adequate dose of L-DOPA or dopamine agonists. A summary of the response, the therapy and dosing regimen employed, and the date of entry into the medical records were recorded in the patient CRF.

9.3.2.4 Multiple system atrophy-specific inclusion criteria

For patients diagnosed with MSA (SDD), satisfaction of the Consensus Committee of the American Autonomic Society and the American Academy of Neurology diagnosis criteria, [Consensus Committee 1996], i.e. a combination of autonomic dysfunction, parkinsonism and ataxia in any combination, the features of which include:

- Parkinsonism (bradykinesia with rigidity or tremor or both), usually with a poor or unsustained motor response to chronic L-DOPA therapy.
- Cerebellar or corticospinal signs.
- Orthostatic hypotension, impotence, urinary incontinence or retention, usually preceding or within 2 years after the onset of the motor symptoms.

9.3.2.5 Progressive supranuclear palsy-specific inclusion criteria

(1) For patients diagnosed with PSP (SDD), documented evidence of a poor or absent response to chronic L-DOPA therapy. A summary of the response, the dosing regimen employed, and the date of entry into the medical records were recorded in the patient CRF.

(2) For patients diagnosed with PSP , satisfaction of the National Institute for Neurological Disorders and the Society for Progressive Supranuclear Palsy (NINDS-SPSP) clinical criteria for diagnosis, [Litvan 1996]:

I *Full compliance with the following criteria:*

- Gradual, progressive disorder
- Onset at age 40 years or later
- Vertical gaze (upwards or downwards, or both gaze) supranuclear palsy*
- Prominent postural instability with falls in the first year of disease onset

*Upward gaze is considered abnormal when pursuit or voluntary gaze, or both, have restriction of at least 50% of the normal range.

II *The following supportive criteria may or may not have been present:*

- Slowing of vertical saccades
- Symmetric akinesia or rigidity, proximal more than distal
- Abnormal neck posture, especially retrocollis
- Early dysphagia and dysarthria
- Early onset of cognitive impairment including at least 2 of the following: apathy, impairment in abstract thought, decreased verbal fluency, utilization or imitation behavior, or frontal release signs.

PS patients were required to conform with all of the general PS inclusion criteria, as well as any other relevant specific criteria listed above (for PD [*de novo* or established patients], MSA, or PSP) to be considered suitable for entry into the study.

9.3.3 Inclusion criteria for definite essential tremor patients

Patients diagnosed with definite ET were considered for selection on the basis of the following inclusion criteria:

(1) Patients of either sex, within the age range 40-80 years

(2) Documentation of the clinical diagnosis as ET

(3) Satisfaction of Findley & Koller definite ET definitions and behavioral classifications for clinical diagnosis, [Findley and Koller 1994], i.e.

- Bilateral postural tremor with or without kinetic tremor, involving hands or forearms, that is visible and persistent

  Note: Tremor of other body parts may be present in addition to upper limb tremor. Bilateral postural tremor may be asymmetric. Tremor is reported by the patient to

be persistent although the amplitude may fluctuate. Tremor may or may not produce disability.

- Relatively long-standing condition (longer than 5 years)

(4) In the opinion of the investigator, the patient understood the study information, instructions and advice, and was able and willing to comply with the protocol requirements, and visits to the study site at the required time-points. Patients had to be judged to be co-operative and give their written informed consent to participate in the study.

ET patients were required to comply with all of the above inclusion criteria to be considered eligible for entry into the study.

9.3.4 Exclusion criteria for all patients and volunteers

All patients/volunteers were excluded from participation in the study if any of the following general exclusion criteria were found to apply:

(1) Use of any concomitant medication that was known or suspected to interact with striatal uptake through direct competition with binding of DaTSCAN™ to DaT.

(2) Presence of any medical condition that was known or suspected to interact with the pharmacokinetics of the test product, or iodine, e.g. renal and hepatic impairment.

Note: For the purposes of this study 'impairment' was defined as:

- Renal impairment - serum creatinine levels 3-fold above the upper limit of the normal range.

- Hepatic impairment - hepatic transaminase 3-fold above, and gamma glutamyl transferase (GGT) 5-fold above the upper limit of the normal range.

(3) Occupational exposure to radiation equal to, or above, 15 mSv per year.

(4) History of abuse, or current abuse, of drugs and/or alcohol.

(5) Participation in a clinical study involving an unlicensed pharmaceutical product within the 3 months prior to screening, and/or an unlicensed/licensed radiopharmaceutical within a minimum of 5 radioactive half-lives prior to screening.

(6) Previous enrolment in this study.

(7) Any laboratory value(s), with the exception of serum creatinine, hepatic transaminase, GGT, pro-thrombin time, and creatine phosphokinase isoenzymes (MB and MM fractions) exceeding the limits of normality by more than 10% if deemed clinically relevant by the investigator within the context of the individual patient/volunteer.

(8) Females of child bearing potential who were not using a medically acceptable form of contraception.

(9) Females who were pregnant or lactating.

Note: A pregnancy test was performed in all cases where there was doubt around the possibility of pregnancy, or was required by the local IEC.

9.3.5 Exclusion criteria for healthy volunteers

Healthy volunteers (no SDD) were excluded if any of the general exclusion criteria or healthy volunteer-specific exclusion criteria were found to apply or if there was a history of psychiatric illness.

9.3.6 Exclusion criteria for Parkinsonian syndrome patients

9.3.6.1 General Parkinsonian syndrome exclusion criteria

(1) Clinical evidence of cerebral vascular disease or presence of cerebral tumor or communicating hydrocephalus confirmed on computed tomography or Magnetic Resonance Imaging if appropriate.

(2) Positive Diagnostic and Statistical Manual of Mental Disorder assessment for dementia.

(3) History of repeated stroke with stepwise progression of Parkinsonian features.

(4) History of repeated head injury.

(5) History of definite encephalitis.

9.3.6.2 Parkinson's disease-specific exclusion criteria

(1) For patients diagnosed with PD (SDD), satisfaction of remaining UKPDS Brain Bank Criteria Step 2- Exclusion Criteria for PD, i.e:

- Oculogyric crises.
- Neuroleptic treatment at onset of symptoms.
- More than 1 affected relative.
- Sustained remission.
- Strictly unilateral features after 3 years.
- Supranuclear gaze palsy.

- Cerebellar signs.
- Early severe autonomic involvement.
- Early severe dementia with disturbances of memory, language, and praxis.
- Positive Babinski sign.
- Negative response to large doses of L-DOPA (if malabsorption excluded).
- 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine exposure.

9.3.6.3 Multiple system atrophy-specific exclusion criteria

There were no specific MSA exclusion criteria applied in this study.

9.3.6.4 Progressive system palsy-specific exclusion criteria

(1) For patients diagnosed with PSP, satisfaction of the NINDS-SPSP clinical criteria for diagnosis, [Litvan et al. 1996], i.e.:

- Alien limb syndrome, cortical sensory deficits, focal frontal or temporoparietal atrophy.
- Hallucinations or delusions unrelated to dopaminergic therapy.
- Cortical dementia of Alzheimer's type (severe amnesia and aphasia or agnosia, according to National Institute for Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria).
- Prominent, early cerebellar symptoms or prominent, early unexplained dysautonomia (marked hypotension and urinary disturbances).
- Severe, asymmetric Parkinsonian signs. i.e. bradykinesia.
- Neuroradiologic evidence of relevant structural abnormality, i.e., basal ganglia or brainstem infarcts, lobar atrophy.
- Whipples disease.

PS (SDD) patients were excluded if any of the general exclusion criteria, PS-specific exclusion criteria, or any other relevant PD- or PSP-specific exclusion criteria were found to apply.

9.3.7 Exclusion criteria for definite essential tremor patients

(1) Satisfaction of Findley & Koller definite ET exclusion criteria and behavioral classifications for clinical diagnosis, [Findley and Koller 1994], i.e:

- Presence of abnormal neurological signs.

  Note: With the exception of tremor and Froment's sign, the full neurological examination should be normal for age.

- Presence of known causes of enhanced physiological tremor including hyperthyroidism.

- Concurrent or recent exposure to tremorogenic drugs or the presence of a drug withdrawal state (see Section 9.4.10.3(b)).

- Direct or indirect trauma to the nervous system within 3 months preceding the onset of tremor. This includes head injury (direct or indirect), and peripheral injury, if the anatomical distribution of injury is the same as that of the tremor.

- Historical or clinical evidence of psychogenic origins of tremor. Clinical features that may suggest non-physiological variations (>1 Hz) in tremor frequency, unusual and inconsistent behavioral characteristics, and spontaneous remissions. Psychiatric or social factors (multiple somatizations, secondary gain, litigation or compensation pending), may support the diagnosis of psychogenic tremor.

- Convincing evidence of sudden onset or evidence of stepwise deterioration.

(2) The patient has first degree relatives diagnosed with PD.

ET (no SDD) patients were excluded if any of the general exclusion criteria or ET-specific exclusion criteria were found to apply.

9.3.8 Withdrawal of subjects from the study or from assessment

Subjects were free to withdraw from the study at any time. The investigator could also withdraw a subject from the study if an illness or AE occurred, if the subject did not co-operate, or for any reason concerning the health or well-being of the subject.

If withdrawal occurred after administration of the DaTSCAN™ but before all evaluations were completed, efforts were made to complete the safety-related evaluations and report the observations as thoroughly as possible. A complete final evaluation was performed at the time of the subject's withdrawal, giving an explanation of the withdrawal. The reason for withdrawal was recorded on the subject's CRF. If the reason for withdrawal was an AE, the subject was monitored until the AE was resolved or the outcome was evident.

9.4 Investigational Medicinal Product

9.4.1 Identity of investigational medicinal product

DaTSCAN™ ([^{123}I] ioflupane) is an isotonic solution for i.v. administration. The active substance, [^{123}I] ioflupane, binds with high affinity to the pre-synaptic DaT protein. The chemical name for [^{123}I]ioflupane is [^{123}I] N-ω-fluoropropyl-2β-carboxymethoxy-3β-[4-iodophenyl] nortropane).

Amersham Health B.V., Eindhoven, The Netherlands, supplied DaTSCAN™ at a concentration of 74 MBq (2 mCi)/mL (0.07 to 0.13 µg/mL of ioflupane) at calibration time in vials containing 2.5 mL. ^{123}I has a physical half-life of 13.2 hours. The product is referenced to 12:00 hours Central European Time 1 day after manufacture. For the 2.5-mL vial, expiry is 7 hours from the activity reference time stated on the label (31 hours from the end of manufacture). In this study, vials were labeled "for clinical studies only".

Sufficient quantities of fully characterized IMP were provided and manufactured, packaged, and labeled in accordance with Good Manufacturing Practice. Shipping of the study drug to the study sites and dispensing of it to each subject was recorded as part of the study documentation.

The investigator maintained accurate records of the receipt of the IMP from the sponsor, including the date of receipt and subject code numbers. Date of examination, batch/vial codes used, activity and volume per administration and start and end time of administration were recorded in each subject's CRF and the radiopharmaceuticals log. All DaTSCAN™ shipping and disposal was logged by each of the parties concerned. In addition, drug accountability was maintained at the study site using a drug accountability log signed and dated by the investigator or delegate.

For information regarding the batches/vials of DaTSCAN™ that were used in this study, refer to Section [16.1.6].

DaTSCAN™ has been authorized for marketing in the European Union since 2000.

9.4.2 Storage

DaTSCAN™ was stored at room temperature (not above 25°C). Appropriate radiation precautions were observed during storage of the agent.

9.4.3 Preparation

Appropriate radiation precautions were observed during preparation of the agent.

9.4.4 Investigational medicinal product administration (route, dose, and dosage schedule)

DaTSCAN™ was injected with the subject supine. After the access into an arm vein had been established, each subject received a single i.v. injection of DaTSCAN™ with a total activity amounting to 111 to 185 MBq (3 to 5mCi). DaTSCAN™ was administered via slow (not less than 15 to 20 seconds) i.v. injection and was followed by a saline flush of approximately 5 mL. The exact amount of activity was measured before injection and was tailored to the particular imaging system involved. Appropriate radiation precautions were observed during use of the agent.

9.4.5 Comparator product

No comparator was used in this study.

9.4.6 Method of assigning subjects to treatment groups

Each subject was assigned to receive DaTSCAN™.

9.4.7 Rationale for dose selection in the study

Refer to Section 9.2.2 for the rationale for the recommended dose range (111 to 185 MBq). The actual activity for each subject was tailored to the specific imaging system used at each site.

9.4.8 Selection and timing of dose for each subject

Each subject received a single i.v. dose of DaTSCAN™ 3 to 6 hours before SPECT imaging, based on the results of an earlier phase 2 clinical study (CY96.FP.II) that showed this to be a suitable window for SPECT imaging.

9.4.9 Blinding

This study was an open-label study in which all subjects were to receive DaTSCAN™. However, the BIE readers were blinded to clinical information about the subjects.

9.4.10 Prior and concurrent therapy or medication

9.4.10.1 Recording of prior and concurrent medications

Details of any prior, concurrent therapy, medication, changes in medication or procedural medication, given to or taken by a subject within 4 weeks before visit S1 were entered in the CRF. The generic or trade name and indication of concurrent or prior medication were also

recorded. All therapy and medication were coded according to the WHO-Drug Dictionary (DD).

9.4.10.2 Procedural medications

Before and after DaTSCAN™ administration each subject received a thyroid blocking preparation, in accordance with each study site's thyroid blocking protocol.

9.4.10.3 Prohibited medications

The investigator had to avoid the concomitant administration of any medication with known or suspected high affinity for DaT that could possibly interact with DaTSCAN™. In line with the Summary of Product Characteristics (SmPC), the list of prohibited concomitant medications stated in the protocol included:

- cocaine (a tropane)
- amphetamine, mazindol and methylphenidate (sympathomimetics)
- benztropine (an anti-cholinergic)
- buproprion (an atypical anti-depressant used for treating nicotine addiction) and sertraline (a selective serotonin reuptake inhibitor anti-depressant) (see also Section 9.2.3).

The minimum washout period for all generally prohibited concomitant medications was 4 weeks before imaging. If a subject was taking prohibited medication that could not be withdrawn, or if during the pre-imaging and imaging phase the use of any prohibited medication became necessary for medical reasons, the subject had to be excluded from participation in the study. If one of the prohibited medications was withdrawn from a subject to satisfy inclusion/exclusion criteria, the investigator first sought agreement of the subject and then implemented an appropriate drug withdrawal regimen.

(a) Parkinson's disease prohibited concomitant medications

In addition to the general prohibited concomitant medications listed above, PD patients were required to have their anti-PD therapy withdrawn for an appropriate period of time determined on a case by case basis prior to the H&Y assessment performed during screening (S1 or S2).

Drug withdrawal in this instance was implemented by the patient themselves following instructions provided by the investigator. PD patients were instructed to take their last dose of anti-PD therapy on the evening before visit S1, i.e. approximately 12 hours prior to the H&Y test.

At some sites this was advised by the investigator and complied with by the patient prior to their signing the study consent form. In all cases, the patient had been informed about the study, had given verbal consent to participate, had agreed to withdraw from their PD (SDD)

medication on the evening prior to visit S1, then had returned at visit S1 and signed the consent form before formally starting study procedures.

(b) Definite essential tremor prohibited concomitant medications

In accordance with inclusion/exclusion criteria for ET patients, [Findley and Koller 1994], investigators were instructed to withdraw all tremorogenic drugs to facilitate the accurate diagnosis of ET.

Where withdrawal of a tremorogenic drug was considered appropriate by the investigator and agreed to by the patient/volunteer for inclusion into the study the investigator was responsible for the implementation, and monitoring of an appropriate drug withdrawal regimen devised on a case by case basis.

9.4.11 Treatment compliance

The subjects received DaTSCAN™ under direct supervision of study personnel. Each injection volume and total radioactivity injected was independently checked and recorded in the CRF. The vial label, containing subject number and vial number, were attached to the subject's CRF.

9.5 Efficacy and Safety Variables and Measurements

Efficacy and safety measurements performed at the study sites and obtained during the course of the study are summarized in the study schedule of events (Table 2).

9.5.1 Efficacy measurements

9.5.1.1 Primary efficacy endpoints

The primary endpoint of the study was the sensitivity and specificity of DaTSCAN™ ([^{123}I]ioflupane) images in detecting SDD, based on visual image assessments by on-site institutional readers and using the clinical diagnosis (made based on standardized robust criteria) as the SOT.

SPECT images were acquired using a variety of devices including both multi and single-headed gamma cameras and multi-detector single slice systems. Each gamma camera system was capable of SPECT acquisition and reconstruction to produce transverse slices including a clear visualization of the striatum (i.e. the head of the caudate nucleus and putamen). The reconstruction algorithm and the collimator type used by each site employing a gamma camera system were not predefined in the final protocol. However, both parameters were recorded in patient/volunteer CRFs with the make and model of gamma camera system used.

The single slice detector systems employed were also capable of imaging the head of the caudate nucleus and putamen. In addition, a standard acquisition protocol was adopted by the

3 sites employing a single slice multi-detector system, (London, Glasgow and Amsterdam), as follows:

Energy window:	140-180 KeV
Acquisition time per slice:	240 seconds
Spacing between slices:	5 mm
Collimator size:	800 hole
Number of scan lines:	9

9.5.1.2 Institutional read

All scans were reconstructed at each site to the highest resolution possible using the software available to the site. The investigator or appointed delegate(s) at each site was responsible for the evaluation of each patient/volunteer image acquired at the site. Evaluation of each image was based on an assessment of uptake of DaTSCAN™ in the striatum in accordance with the following classifications:

Table 3 DaTSCAN™ SPECT Visual Image Assessment Classifications

DaTSCAN™ Image Classification	Criteria
Normal	Normal images were characterized by uptake of the tracer in both right and left putamen and caudate nuclei. The image was largely symmetrical with approximately equal levels of uptake on both left and right sides. Activity was contained close to the center of the image forming 2 crescent shaped areas of uptake.
Abnormal, type 1	Uptake is asymmetric with normal or almost normal putamen activity in 1 hemisphere and a more marked change on the other side.
Abnormal, type 2	Uptake was significantly reduced in the putamen on both the right and left sides. Activity was confined to the caudate nuclei and forms 2 roughly symmetrical, circular areas.
Abnormal, type 3	Uptake was virtually absent from both putamen and caudate nuclei on each side of the brain resulting in a significant reduction in contrast and the visualization of background activity throughout the rest of the image.

The classification attributed to each image was recorded by the investigator or appointed delegate in the patient/volunteer CRF. For efficacy analyses, the 3 abnormal image types were combined to allow a dichotomous division of images into "normal" or "abnormal" categories.

Electronic raw data were supplied by all sites to the study site in Amsterdam for uniform reconstruction using an identical color scale and format for each image. The resultant hard copy images were then randomized and blinded using a numbering system generated by BIOS International Ltd. to protect the identity of the originating study site.

9.5.1.3 Secondary efficacy endpoints

The secondary efficacy endpoints identified for this study were:

- Sensitivity and specificity of visual assessment of DaTSCAN™ striatal uptake as determined by the 'Blinded Read' (BIE).

- Sensitivity (response rate in PS subjects) was determined overall by H&Y grade and by UPDRS score category (<22, ≥22).

- Inter-reader agreement was performed for the 5 BIE readers and on-site reads with respect to the DaTSCAN™ SPECT visual assessment findings (abnormal/normal).

- Semi-quantitative assessment of regions of interest (ROIs).

9.5.1.4 Clinical diagnosis used in the on-site investigator and BIE reads (standard of truth)

Although the SOT used in this study report was not explicitly discussed in the original European clinical study report (CSR) or protocol, the study used well-accepted criteria of diagnosis as selection criteria to assure that subjects had (or did not have) conditions known to be associated with striatal dopaminergic deficits. These diagnoses served as the SOT to permit validation of the DaTSCAN™ image assessments, and they were performed before DaTSCAN™ imaging. Patients had to be diagnosed as having PS (PD, MSA, or PSP; all are known to be associated with SDD), ET (no SDD), or a normal status (as a healthy volunteer [no SDD]).

Subjects with a diagnosis of PS (SDD) had to meet step 1 of the UKPDS Brain Bank criteria, and had to meet additional criteria depending on the type of PS. The UKPDS Brain Bank criteria for PS and PD, the MSA diagnostic criteria, the PSP criteria, and Findley and Koller criteria are all criteria of acknowledged validity based on consensus opinion of experts. Patients with PS are known to have SDD based on the known pathophysiology of this syndrome, and patients with ET (as well as the healthy volunteers) are known to not have SDD.

9.5.1.5 Blinded read

Electronic raw data were supplied by all sites to the study site in Amsterdam for uniform reconstruction using an identical color scale and format for each image. The resultant hard copy images were then randomized and blinded using a numbering system generated by BIOS International Ltd. to protect the identity of the originating study site.

A BIE panel, consisting of 5 of 13 investigators involved in the study, was selected and included 1 neurologist with limited experience in the assessment of DaTSCAN™ images (Dr. D. Grosset, Glasgow), and 4 nuclear medicine physicians each with experience in the assessment of DaTSCAN™ images (Dr. D.C. Costa, London; Professor E. van Royen, Amsterdam; Professor R. Dierckx, Gent; and Professor K. Tatsch, Munich).

Blinded images were produced for each patient/volunteer who underwent DaTSCAN™ administration and had an available image, resulting in the preparation and evaluation of 220 blinded images. Evaluation of each blinded image was based on a visual assessment of uptake of DaTSCAN™ in the striatum in accordance with the classifications in Section 9.5.1.2. Each panel member had reference to the example images as the blinded images were presented.

For each image the Blinded Reader was asked to first assess whether or not the image presented was normal or abnormal. If the image was judged to be abnormal, the Reader was asked to choose the appropriate image type (1-3). The classification attributed to each blinded image was recorded in an appendix to the CRF using the randomization number assigned to each blinded image as an identifier.

At each Blinded Read session, the panel member was accompanied by a technician from the core lab. The technician was responsible for the preparation of the blinded images, and instructed each Blinded Reader with the same background technical information. After this basic instruction, the images were presented in numerical order with no further discussion. The core lab technician was responsible for the presentation of each blinded image. A clinical monitor (not the same person at each reading) from the sponsor company acted as scribe for the panel member.

Each Blinded Read session took on average 90 minutes to complete.

The protocol stated that a Mismatch Panel would be convened to discuss cases of disagreement between the Blinded Readers. Unfortunately, due to professional pressures within the Blinded Readers it was not possible to conduct this 'Mismatch Panel'. Therefore, it was decided that if 3 or more readers classified an image as either normal or abnormal (independent of subtype), that would represent the 'consensus' (majority) assessment. This was not a consensus read in the usual sense – each reader reviewed images independent of the other readers and there was no discussion of images among readers; it was actually a majority assessment.

9.5.1.6 Semi-quantitative analysis

Electronic raw data provided to the study site in Amsterdam were further utilized to generate data for the semi-quantitative assessment. Semi-quantitative assessment, based on ROI analysis, was used as a secondary study endpoint, and was conducted for all 220 images. Each of the semi-quantitative assessments conducted are detailed below.

Primary semi-quantitative outcomes

- Specific uptake in striatum, caudate nucleus and putamen.

Secondary semi-quantitative outcomes

- Ratio of specific to non-specific uptake for striatum, caudate and putamen.
- Asymmetry Index - Assessment of asymmetry between ipsilateral and contralateral (relative to the side of first onset of subject's symptoms) striatal uptake.
- Ratio of specific uptake in the putamen compared with that in the caudate nucleus.

The results of each semi-quantitative analysis performed were compared to the original diagnosis and stage of disease.

9.5.1.7 Mismatch analysis

All "mismatches" between DaTSCAN™ image assessment and clinical diagnosis were to be referred to a committee comprised of 5 experienced clinical neurologists selected from the investigators involved in the study. Anonymized case notes were to be provided for all mismatches, together with an equal number of non-mismatches to prevent bias, and a consensus diagnosis obtained. The DaTSCAN™ images were not to be provided for review by the committee. A qualitative description of the results obtained was to be provided as an addendum to the report/appendix. However, as noted above, this analysis was not conducted because the investigators were not available.

9.5.2 Safety measurements

9.5.2.1 Adverse events

An AE was defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP. Only symptoms/signs that began or worsened in severity after IMP administration were recorded as AEs in the CRF (within the study period, i.e., up to 48 to 96 hours after DaTSCAN™ administration).

The subjects were closely observed and questioned for any kind of AE during the study procedures and throughout the study period with non-leading questioning (e.g., How do you feel?). The subjects were instructed to immediately report any symptoms and signs to the study staff (i.e., between formal observations).

Serious Adverse Events

A serious AE (SAE) was defined as any AE that:

- Resulted in death.
- Was immediately life-threatening.
- Required inpatient hospitalization or prolongation of existing hospitalization.
- Resulted in persistent or significant disability or incapacity.
- Was a congenital anomaly or birth defect.
- Was another important medical event.*

*Other important medical events that may be considered an SAE, when based upon appropriate medical judgment, include events that may jeopardize the subject and may require medical intervention to prevent one of the outcomes listed above.

Adverse event and serious adverse event reporting

All AEs reported by the subject or observed by the hospital personnel were reported in the CRF. The following information regarding each AE was obtained: date and time of onset and resolution (duration), intensity and causality (defined below) whether it was serious (previously defined), any required treatment or action taken, outcome, relationship to the administration of DaTSCAN™, and whether the AE caused withdrawal from the study.

All AEs were recorded using accepted diagnoses whenever possible. If an AE had already been reported, it was not necessary to report each individual sign and symptom of that AE as a separate AE. For example, if myocardial infarction was reported as an AE, there was no need to report elevated creatine phosphokinase and abnormal ECG, or other related signs, symptoms, or laboratory values as separate AEs. However, if both occurred in isolation and myocardial infarction was not diagnosed, then each event was reported as an AE.

The intensity of all AEs was graded as mild, moderate, or severe using the definitions described below.

Mild: Tolerable

Moderate: Interferes with normal activity

Severe: Incapacitating (causes inability to perform usual activity or work)

Causality was assessed as probably related, possibly related, unlikely to be related, and unrelated. Every effort was made by the investigator to explain each AE reported, and to assess its relationship, if any, to DaTSCAN™. The degree of certainty with which an AE was attributed to test product (or alternative causes, e.g. natural history of the underlying disease, concomitant therapy) was determined by how well the experience could be understood in terms of the known pharmacology of DaTSCAN™, and documented reactions of a similar nature related to DaTSCAN™ or other radionuclides.

The investigators were instructed to closely monitor each subject who experienced an AE (whether ascribed to the injection of DaTSCAN™ or not) until the outcome of the AE had been determined. In addition to the investigator's own description of the AEs, each AE was encoded according to a well known dictionary of medical codes (MedDRA).

SAEs were recorded in the subject's CRF if they occurred as follows:

- After a subject first received an injection of DaTSCAN™ and throughout the subject's follow-up period*, whether or not considered related to the IMP.
- After the subject's follow-up period and for which a causal relationship to the IMP could not be ruled out.

*Follow-up period is defined as the protocol-stipulated period or the duration of the subject's participation in cases where the subject was prematurely withdrawn.

All serious and non-serious AEs were followed for a final outcome until the end of the follow-up period. An outcome of "unknown" was not considered to be an acceptable final outcome. An outcome of "not yet resolved" was an acceptable final outcome for non-serious AEs at the end of a subject's participation in a study, and for SAEs at database lock.

The sponsor reported all SAEs to local health authorities, IECs and investigators as required by local regulations and sponsor standard operating procedures (SOPs).

Study sites were instructed to report SAEs to the sponsor within 24 hours of becoming aware of the SAE.

9.5.2.2 Clinical laboratory variables

Detailed laboratory results are not addressed in this report but were presented in Section [12.4.1] of the original European CSR. Blood and urine samples were collected at visit S1 to assess patient/volunteer eligibility, prior to DaTSCAN™ administration, and at visit F1, 24 to 72 hours post injection. The laboratory tests measured are listed in Table 4.

Table 4 Laboratory Measurements

Serum Biochemistry	Hematology	Urinalysis
Creatinine	Hematocrit	Bilirubin
Bilirubin (total)	Hemoglobin	Protein
Albumin	Red blood cell (RBC) count	Urobilinogen
Aspartate aminotransferase (ASAT)	White blood cell (WBC) count	Glucose
Alanine aminotransferase (ALAT)	WBC Differential	Ketone
Alkaline phosphatase (AP)	Platelet count	Occult blood
Gamma-glutamyltransferase (GGT)	Prothrombin time	Specific gravity
Sodium		Leukocytes
Potassium		pH
Lactate dehydrogenase (LDH)		
Creatine phosphokinase (CPK)[a]		

[a] If total CPK was abnormal then the MB and MM fractions were analyzed

Serum creatinine and hepatic transaminase levels 3-fold above the upper limits of normality, and GGT levels 5-fold above the upper limits of normality at S1 resulted in the exclusion of the patient/volunteer from the study. For all other laboratory results, with the exception of prothrombin time, values of $\geq$ 10% outside the limits of normality were reviewed by the investigator in the context of the individual patient/volunteer; any such abnormality deemed clinically relevant resulted in the patient/volunteer's exclusion from the study.

Prothrombin time for all patient/volunteers was assessed at the end of the study. Samples collected at each visit were processed accordingly and stored at or below -20°C until the end of the study. All samples were then transported on dry ice to Medi-Lab for analysis. Any prothrombin time result found to be 10% above the upper limits of normality, and considered to be clinically relevant, was reported as an AE. Each site provided a partial prothrombin time specimen for each study time point for most subjects. The exception to this was London where generally the pre-imaging and follow-up specimens were not collected.

Creatine phosphokinase-MB and -MM fractions were assessed only if total creatine phosphokinase was found to be 10% above the upper limits of normality and deemed clinically relevant in the context of the patient/volunteer. Analysis of creatine phosphokinase isoenzymes was conducted in batches by the central laboratory (MediLab and Spranger & Kloss for the UK and Europe, respectively) using electrophoresis. Any creatine phosphokinase isoenzyme fractions found to be 10% outside the limits of normality and deemed clinically relevant were reported as AEs.

The signed and interpreted laboratory results were kept together with the subject's CRF as supplemental pages, both centrally and at the site.

9.5.2.3 Vital signs

Detailed vital-signs results are not addressed in this report but were presented in Section [12.5] of the original European CSR. Vital-signs measurements occurred during visit S1 and during visit F1, 24 to72 hours post DaTSCAN™ injection, using standard methods. Vital-signs measurements included measurement of heart rate and systolic and diastolic blood pressures. Before vital signs were measured the subject rested for at least 5 minutes. The subject was in the same position each time vital signs were measured. Blood pressure was measured from the arm contralateral to the site of IMP administration, whenever possible. Systolic and diastolic blood pressure (blood pressure in millimeters of mercury [mm-Hg]) was measured by means of a sphygmomanometer. Heart rate (pulse in beats per minute) was measured at the radial artery by manual palpitation.

9.5.2.4 Electrocardiograms

A more detailed description of ECG results are not addressed in this report but were presented in Section [12.5] of the original European CSR. ECG was measured during visit S1 and during visit F1, 24 to 72 hours post DaTSCAN™ injection, using standard methods. Standard 12-lead ECG recordings were completed for each patient/volunteer over a 20-minute period at S1 and F1. ECG traces were reviewed by the investigator or appointed delegate. Subject management decisions were based on the 12-lead ECG findings.

9.5.2.5 Physical examinations

Physical examinations included measurement of resting vital signs (blood pressure and pulse) and 12 lead ECG. Results are found in Table [15.2.16] of the original European CSR but were not addressed in-text in that report.

9.5.2.6 Injection site monitoring

The injection site was evaluated at visit F1. Abnormal injection site findings could include, but were not limited to radiopharmaceutical extravasation, bleeding, hematoma, redness, and infection.

9.5.3 Appropriateness of measurements

All assessments and measurements were appropriate and regarded as standard medical practice.

9.6 Clinical Data Management

All clinical monitors received thorough training with respect to the final protocol and CRF in accordance with the monitoring guidelines. An annotated CRF was produced specifically for the purposes of the study. All initiation visits were standardized with regard to content and format, and clinical monitors were issued with standard source data verification forms that were completed for each patient to verify the source data.

Data management was conducted by BIOS International Ltd., a CRO based in the UK. Statistical analyses included in this study report were performed by i3 Statprobe, a CRO based in the United States. Data management and programming were carried out as described in the CRO's SOPs for clinical studies. Data from the CRF were double entered using a verified system (where data were entered by 2 independent people into a single file, but the second person was unable to view the first entry) using Keydata (Version 1.05.15). Details of who carried out primary and secondary data entry were logged and checked to ensure that the same operator did not undertake both entries. Any changes made to the database were logged in an audit trail; changes arising from secondary data entry were manually checked against the original CRF by an independent person. Any instances where the data entered into the computer differed from that on the CRF was either documented in the data manual, or on a query form for retention at the study site.

SAS® (Version 6.12) software validation programs were produced to ensure the plausibility and consistency of the data. Where necessary, queries were raised for resolution. Once no further CRFs or queries were outstanding, the data listings from SAS were audited against the CRF by the BIOS Quality Assurance department; 5% of CRFs were checked on 29 May 1998. A total of 4,213 variables were audited with an error rate of 0.02%. The database consequently passed QA inspection, the acceptable rate being pre-defined as less than 0.1%.

Upon completion of recruitment at each study site an independent auditor, Good Clinical Research Practices Limited, were contracted to conduct on site GCP audits. Each audit consisted of a review of the investigator site file to ensure archiving of essential documents, a review of product accountability procedures at site, and verification of CRF data against source documents. Copies of the audit certificates issued for each site are provided in Appendix [16.1.8].

In addition to site audits, Good Clinical Research Practices Limited also conducted an in-house sponsor audit consisting of a review of the central study master file, to ensure archiving of essential documents, and a review of archived CRF data. A copy of the audit certificate issued for the in-house audit is also provided in Appendix [16.1.8].

Documentation of inter-laboratory standardization methods and quality assurance procedures are provided in Appendix [16.1.10].

Data management for the US analysis was carried out by i3Statprobe, a CRO based in the US. i3Statprobe's programming procedures complied with the regulatory guidelines (e.g., ICH-GCP). i3Statprobe received the raw datasets containing all information captured in the study CRF from the sponsor. A statistical programmer reviewed the CRF and determined how data variables linked to each section in the CRF. Once the programmer was comfortable with the location of the variables in the CRF, the programmer created specifications for reassigning variable names based on CDISC SDTM-compliant naming conventions. The programmer then created a CDISC SDTM-compliant dataset. The specifications were then validated by an independent programmer, who also created a CDISC SDTM-compliant dataset using the specifications and then compared that dataset with the raw dataset to ensure that the mapping was correct.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

The full Statistical Report is appended in Section [16.1.9] of this report.

9.7.1 Statistical plans

Tabulations of summary statistics, graphical presentations, and statistical analyses were performed using SAS® Software (Version 9.0 or later).

The planning and reporting of statistical analyses for this US report were carried out as described in the CRO's SOPs governing clinical studies.

All continuous variables were summarized by the following descriptive statistics: number of subjects (N), number of subjects in a subgroup (n), mean, standard deviation (SD), median, minimum, and maximum. Discrete variables were summarized by counts and percentages. All statistical tests were carried out at the 5% level of significance, unless otherwise specified. All p-values presented were two-sided and set at a 5% level of significance. All analysis of variance (ANOVA) models used type III sums of squares. All response rates were presented with a one sided 95% confidence level (CL) of the lower boundary, and all mean differences with two-sided 95% CLs.

9.7.1.1 Study population variables

(a) Disposition of subjects

The following information on subject disposition was provided:

- Number of subjects enrolled.
- Number of subjects who received DaTSCAN™ (i.e., who were dosed).
- Number of subjects included in the safety analysis.
- Number of subjects included in the efficacy analysis.

Completion status was tabulated, together with reason(s) for non-completion and reason(s) for withdrawal in total and by site.

(b) Demographic data

The demographic data was summarized using descriptive statistics. The following parameters were used:

- Age
- Sex
- Race
- Height and Weight
- Screening Systolic and Diastolic Blood Pressure
- Screening Pulse Rate
- Screening H&Y Assessment
- Screening Clinical Diagnosis (ET [no SDD], PD [SDD], MSA [SDD], PSP [SDD], or healthy volunteers [no SDD])

Summaries were done for the safety population overall and by diagnosis.

9.7.1.2 Determination of the safety and efficacy population

Three analyses populations were defined; 2 efficacy patient populations and a patient/healthy volunteer safety population, as follows:

(a) Determination of the safety population

All patients/volunteers enrolled who received DaTSCAN™ were included in the assessment of safety parameters. Protocol compliance was assessed by applying the following criteria:

- Patient/volunteer elected to withdraw from the study for reasons other than experience of adverse events.
- Lack of co-operation with study requirements.
- Use of prohibited concomitant medication between screening and the imaging phase of the study, and/or during the imaging phase of the study.
- Patient/volunteer did not comply with the inclusion/exclusion criteria.

- SPECT imaging performed outside the acceptable time range for DaTSCAN™ imaging, i.e. less than 3 hours and more than 6 hours post-injection.
- Patient/volunteer did not receive 111-185 MBq.
- PS patients did not have an appropriate response to L-DOPA therapy.

(b) Intention-to-diagnose

All subjects enrolled into the study with an available DaTSCAN™ image were included in the intention-to-diagnose (ITD) population for the evaluation of efficacy. This population included withdrawn patients who had a DaTSCAN™ image. This is a more realistic representation of the general population as it included those subjects with images outside the dose range and the imaging time window. Analyses from the ITD patient population are considered secondary and have been performed for all primary and secondary efficacy endpoints.

(c) Per-protocol

All subjects enrolled with an available DaTSCAN™ image who did not violate the protocol in any way were included in the per-protocol (PP) population for the evaluation of efficacy. To be included in this analysis a subject had to conform to the following protocol criteria:

- All entry criteria for the ITD population.
- All study inclusion and exclusion criteria as appropriate to the subject's condition.
- The subject refrained from using prohibited concomitant medication between the screening and the imaging phases of the study, and/or during the imaging phase of the study.
- A SPECT image was performed within the acceptable time range for DaTSCAN™ imaging, i.e. between 3 and 6 hours post injection.
- The injected dose of radioactivity was between 111 and 185 MBq.
- The subject was not withdrawn from the study for reasons other than an AE.

Analyses from the PP patient population were considered primary and were performed for all primary and secondary efficacy endpoints.

9.7.1.3 Efficacy variables

(a) Primary efficacy endpoint

The primary efficacy variable described in Section 9.5.1.1 was analyzed as follows for both the ITD and PP populations; the results from the PP population were considered primary.

Parkinsonian Syndrome

The response rate for DaTSCAN™ striatal uptake for patients with PS (SDD) was calculated as follows to assess the sensitivity of the test product:

$$\text{Response Rate (Sensitivity)} = \frac{\text{No. of Abnormal SPECT Images}}{\text{(No. of Abnormal SPECT Images + No. of Normal SPECT Images)}}$$

The effect of the H&Y rating scale on the binary response of Abnormal/Normal striatal uptake for PD patients only was analyzed using the Wilcoxon rank sum test.

Essential Tremor

The response rate for DaTSCAN™ striatal uptake for patients with the clinical diagnosis of ET (no SDD) was calculated as follows to assess the specificity of the test product:

$$\text{Response Rate (Specificity)} = \frac{\text{No. of Normal SPECT Images}}{\text{(No. of Normal SPECT Images + No. of Abnormal SPECT Images)}}$$

The effect of site and age (by decade) differences on the binary response of Abnormal/Normal striatal uptake, for both the PS (SDD) and ET (no SDD) groups of patients was analyzed using Fisher's exact test and the Wilcoxon rank sum test, respectively. Mismatches were defined as normal striatal uptake for PS (SDD) patients or abnormal striatal uptake for ET (no SDD) patients.

(b) Secondary efficacy endpoints

The following secondary analyses were defined and performed on both the ITD and PP populations, the results from the PP population were considered primary.

(i) Blinded Read Visual Assessment

In addition to the institutional read carried out at the study sites a central Blinded Read was performed. The Blinded Read images were analyzed as for those of the institutional read. Disagreements between the results of both readings were summarized descriptively.

(ii) Semi-quantitative Assessments

For each patient/healthy volunteer enrolled in the study the following semi-quantitative assessments of the ROI data were calculated.

(iii) Specific Uptake

The specific uptake of DaTSCAN™ was recorded for the striatum, caudate and putamen, for both the left and right sides of the brain.

(iv) Ratio of Specific to Non-specific Uptake

The ratio of specific to non-specific uptake of DaTSCAN™ was recorded for striatum, caudate and putamen, for both the left and right sides of the brain.

(v) Asymmetry index

An assessment was made of the asymmetry of DaTSCAN™ uptake between ipsilateral and contralateral striatum. A separate presentation of the asymmetry index for caudate and putamen were also considered.

(vi) Putamen/Caudate Ratio

The ratio of specific DaTSCAN™ uptake in the putamen/caudate, for both the left and right sides of the brain.

ANOVA techniques were used to analyze all of the above. For all but the asymmetry index, separate models were produced for the left and right sides of the brain. For the asymmetry index, 1 model was produced.

For each model, the clinical diagnosis (healthy volunteers [no SDD], PS (SDD) or ET [no SDD]) and stage of disease (H&Y assessment) were fitted as factors.

9.7.1.4 Safety variables

No formal statistical analysis of safety for patient/volunteer data was performed. Descriptive summaries of the data were presented.

9.7.2 Determination of sample size

The sample size estimation was based on a one-sided 5% level of significance with a power of 80%. Assuming 95% of PS (SDD) patients have an abnormal DaTSCAN™ striatal uptake, 118 PS (SDD) patients were required to give a maximum allowable deviation of 5%. In addition, assuming 95% of ET (no SDD) patients (control group) have a normal DaTSCAN™ striatal uptake, 30 ET (no SDD) patients were required to give a maximum allowable deviation of 10%. A total of 148 evaluable (PP) patients were therefore planned for recruitment. All withdrawals due to protocol violations were to be replaced to meet the target number of evaluable patients. The assumption that 95% of PS (SDD) subjects would have abnormal DaTSCAN™ uptake is equivalent to assuming that the sensitivity of DaTSCAN™ SPECT images is 95%. Similarly, the assumption that 95% of non-PS subjects would have normal DaTSCAN™ uptake is equivalent to assuming that the specificity of DaTSCAN™ is 95%.

In addition to the 148 evaluable patients, each center was requested to recruit 6 healthy volunteers (no SDD) for the sole purpose of the creation of a normal database. These subjects were also included in the safety analysis.

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Protocol Amendments

A total of 4 protocol amendments were issued subsequent to the final protocol. Amendments 1 through 3 (9 July 1997, 15 July 1997, and 17 September 1997, respectively), represented logistical and administrative changes/clarifications to the protocol and CRF only. In accordance with the guidelines set forth in the ICH-GCP, such amendments were not routinely submitted to local IECs for review, unless specifically requested as part of the local IEC SOPs or by the investigator.

Amendment 1 corrected addresses and qualifications for 3 investigators. Amendment 2 clarified eligibility criteria based on laboratory results and concomitant medication use. Amendment 3 removed the standard tapping test as part of the L-DOPA challenge test because the standard tapping test was not routinely used in clinical practice. Text regarding supportive diagnostic criteria for the diagnosis of PSP was also corrected.

Protocol Amendment 4 (27 November 1997) represented a change to the study design impacting on the evaluation of primary and secondary endpoints, and as such, this amendment was submitted to each local IEC for review. This amendment removed the need to record counts on SME scanners, corrected the description of abnormal image types 1 and 3, and provided new example images that were consistent with the corrected descriptions of image types 1 and 3.

9.8.2 Other Changes

As discussed above, the target number of subjects was 184 (148 patients (118 with PS (SDD) and 30 with ET (no SDD) and 36 HV). The actual number of subjects screened for inclusion into the study was 250 (212 patients and 38 HV). Of the 212 patients, 179 were diagnosed with PS (SDD) and 33 were diagnosed with ET (no SDD). It was necessary to screen more subjects than originally planned in an attempt to account for a drop-out rate that was higher than anticipated, and to obtain the desired composition of PS subjects. The target PS composition was based on PS demographics: 82% PD, 10% MSA, and 8% PSP patients. The actual figures were 82% PD, 12% MSA, and 6% PSP. A decision was taken to stop study recruitment with these figures, as these numbers were considered adequate to proceed with the analyses.

Each of the study sites recruited 6 healthy volunteers except Glasgow (site number 003), which recruited 8 subjects to account for 2 unevaluable subjects who withdrew consent to proceed.

9.8.3 Pre-imaging screening visit

Site number 004 (Amsterdam/Nijmegen) did not conduct pregnancy testing as the local IEC did not allow this to be performed; in the Netherlands this is judged to be an infringement of

personal freedom. None of the female subjects at this site were of child-bearing potential, being either post-menopausal or having undergone hysterectomy.

Upon completion of the screening visit (S1), arrangements were made for all eligible patients/volunteers to return to the site within a 3 week period for test product DaTSCAN™ administration and SPECT imaging. Subject 155 was screened but then went on holiday, which took her outside of this time window. Subject 251 had a prolonged interval between screening and imaging. These subjects were re-screened, effectively re-entering the study as Subject Numbers 187 and 254, respectively.

9.8.4 Test product administered

The actual amount of radioactivity administered to patients/healthy volunteers during this study was in the range 111.30 - 201.11 MBq in a volume of 1.0 - 2.63 mL. On further investigation, it became clear that 4 of the 6 study sites (Marburg, Munich, London and Gent) had administered more than 185 MBq to a total of 47 of their study patients/volunteers.

- Marburg had 16 subjects who received >185 MBq of radioactivity. All subjects were administered with 2.50 mL DaTSCAN™ as advised in the protocol; however 10 of these subjects were injected before the reference time of 12.00 Central European Time. The highest dose of radioactivity injected was 201.11 MBq.

- Munich had 6 subjects who received >185 MBq of radioactivity. Three of these subjects were administered with 2.50 mL DaTSCAN™ as advised in the protocol, with 2 receiving test product before the reference time. The remaining 3 subjects received 2.30 mL of test product again before reference time. At this study site no subject received greater than 185.66 MBq.

- London had 15 subjects who received >185 MBq of radioactivity. These subjects were administered with a volume in the range 1.90-2.63 mL of DaTSCAN™. All subjects however were injected before the reference time (between 48 minutes and 2 hours 45 minutes). The highest dose of radioactivity injected was 200.99 MBq.

- Gent had 10 subjects who received >185 MBq of radioactivity. All subjects were administered with 2.50 mL as advised in the protocol and all 10 were injected before the reference time of 12.00h Central European Time. The highest dose of radioactivity injected was 193.60 MBq.

The increased dose of radioactivity received by the above subjects did not exceed 10% above the upper limit of the prescribed range.

SPECT imaging was performed between 3 to 6 hours post DaTSCAN™ injection except in the case of 4 subjects. Subjects 126, 219, 226, and 259 had their SPECT imaging start time less than 3 hours post DaTSCAN™ injection.

The maximum volume of test product administered was intended to be 2.5 mL. Subjects 113, 124, 138, 147, 120, 129, 130, and 149, all from the London site, had volumes in excess of this noted as having been administered.

All of the above subjects were excluded from the per-protocol analysis but included in the ITD analysis.

Refer to Appendix [15.2.11] in the European CSR for the amount of DaTSCAN™ administered/SPECT imaging times.

9.8.5 Prohibited concomitant medications

A number of subjects received prohibited medications during the study. These were identified subsequent to DaTSCAN™ administration and SPECT imaging so therefore were not generally withdrawn as intended. These subjects were however excluded from the PP analysis as protocol violators, but were included in the ITD analyses.

A full listing of subjects who violated the protocol by taking prohibited concomitant medications is provided in Section [10.2] of the original European CSR.

9.8.6 Institutional read

Results from the institutional read represented the primary endpoint for the study. The investigator or appointed delegate(s) at each site was responsible for the evaluation of each patient/volunteer image acquired at the site. Evaluation of each image was based on an assessment of uptake of DaTSCAN™ in the striatum in accordance with the classifications previously described in Section 9.5.1.2.

Example images of these classifications were provided in 2 editions. Some subjects had the institutional read performed on their images prior to the 2nd edition examples being made available. Where this was the case, the institutional read was re-evaluated for those subjects using the latest edition images.

9.8.7 Blinded Read

A panel of 5 readers was judged to be advantageous in avoiding a tied result. The study protocol pre-defined the Blinded Read panel to include 2 neurologists, 1 with and 1 without experience of DaTSCAN™. In addition, it was the intention that 2 nuclear medicine/imaging specialists participate in the Blinded Read, 1 with and 1 without DaTSCAN™ image experience. However, it was subsequently judged to be more representative of the intended use of the product to include a greater proportion of nuclear medicine/imaging specialists. Therefore, the actual study Blinded Read panel consisted of 4 nuclear medicine/imaging specialists and 1 neurologist.

9.8.8 Mismatch analysis

A mismatch analysis was not performed as described in Section 9.5.1.7. It was the intention, according to the protocol, to facilitate the mismatch discussion immediately after the Blinded Read with the same panel. As the logistics of the Blinded Read panel changed from the intended format it was decided to follow up each mismatch with the corresponding study site to elicit further data where possible.

The Reporting and Analysis Plan in existence at the start of study enrolment required some amendment to clarify changes to the Blinded Read analyses as described below.

Any changes made to the analyses specified in the protocol are detailed in the statistical report provided in Section [16.1.9], and were made prior to data being made available for analysis.

All analyses specified in the original statistical analysis plan were analyzed as planned with the following exceptions:

(1) A central panel Blinded Read was not convened. Instead, 5 of the study investigators were chosen to perform a Blinded Read on images obtained from all patients/healthy volunteers in the study (refer to Section 9.5.1.5 for more detail). A single "consensus" blinded read assessment was produced for each subject using the majority of the 5 individual assessments (i.e., if 3 or more of the BIE readers reported the same assessment, that assessment was taken to be the "consensus" (majority) assessment for the subject).

(2) Prior to performing the semi-quantitative analyses, study site was added as a factor to the models. In addition, the validity of pooling results across sites was assessed by testing for interaction between study site and each semi-quantitative assessment.

The semi-quantitative analyses were not adjusted for stage of disease (H&Y assessment). It was realized at the analysis stage that the H&Y assessment was only recorded for the PD patients hence including the term in the model would have excluded all other subjects.

9.8.9 Changes to the statistical analysis plan for the US revision of the clinical study report

Although demographic results were categorized according to patient population group, this was not specifically stated in the US statistical analysis plan as it was in the European CSR.

The AEs were coded according to MedDRA Version 11.0 and were the only safety summaries produced for the US submission.

The conversion of data to CDISC-compliant format is described above in Section 9.6.

The following changes to the efficacy analyses were made for the US submission:

- Primary Efficacy Variable(s): The revised primary endpoints of the study were the sensitivity and specificity of the on-site institutional read of SPECT images in detecting or excluding a SDD as indicated by the clinical diagnosis at entry, which was used as the SOT. The original endpoints were the sensitivity and specificity for differentiating between subjects with PS and ET, i.e., differentiating between diagnoses. However, it is now clear that while a diagnosis of PS is a marker for a SDD, a SDD is not specific for PS but could also be present in other disorders (DLB, for example). Therefore, DaTSCAN™ images by themselves do not provide a definitive diagnosis. Rather, they detect or exclude a SDD, and this information, along with clinical information and the clinical context, may assist the physician in making a diagnosis. A diagnosis of PS was taken to indicate the presence of a SDD, and a non-PS diagnosis was taken to indicate the absence of a SDD; these assumptions are well supported by numerous autopsy studies published in the medical literature. The exact 95% confidence interval (CI) was calculated for both sensitivity and specificity. All statistical tests were two-sided with a 5% level of significance.

- Secondary Efficacy Variable(s): In the Blinded Read, images were analyzed as in the institutional read. Each blinded reader's assessments were included in 1 overall summary. A "consensus" (majority) blinded read assessment was defined as agreement of a majority (3 or more) of the blinded readers. The "consensus" assessment was analyzed as described for the primary variable. Only subjects with "consensus" reads were included in this analysis. The sensitivity (response rate in this population; equal to the number of abnormal reads divided by the total number of reads) for the institutional read and the "consensus" (majority) read was calculated along with the 95% CI. Sensitivity was also determined for subjects in each H&Y grade and for subjects in each UPDRS category (<22, ≥ 22). A Fisher's exact test was performed to check for a significant difference in sensitivity across H&Y and UPDRS categories. Specificity was also determined for the BIE visual image assessments; however, because H&Y and UPDRS scores were collected only for patients with PS, no analysis of specificity vs. these score was conducted.

- Inter-reader Agreement: Agreement between each pair of on-site and BIE readers with respect to the SPECT visual assessment findings (abnormal/normal) were assessed using Cohen's kappa (κ) coefficient of agreement between the readers with 95% CIs. Although the maximum value for the κ coefficient was 1, it was possible for the upper limit of these CIs to exceed 1 since the calculation used an approximation (based on the normal distribution). In these cases, κ values >1 were to be interpreted as 1 (i.e., perfect agreement). Kappa was ≤ 0 when the observed agreement is less than or equal to chance and it equals 1 when there was perfect agreement. Higher κ value indicated stronger the agreement.

10 STUDY SUBJECTS

10.1 Disposition of Subjects

10.1.1 Disposition of subjects

Table 5 and Figure 4 summarize data on the disposition of subjects. In total, 250 subjects were screened and 224 (89.6%) were included (defined as any patient receiving the IMP) into the study and evaluable for safety. Of the 26 subjects that discontinued prior to dosing, 17 (6.8%) withdrew informed consent, 2 (0.8%) were withdrawn by the investigator, and 7 (2.8%) were found to have protocol violations including prohibited medication use, tremor for less than 5 years, abnormal labs, bowel cancer remission, withdrawn in error, no L-DOPA challenge, and an unclear diagnosis.

Of the 224 subjects dosed, 223 completed the study and were evaluated in SPECT BIE. One subject withdrew consent prior to study completion. An additional 3 subjects were excluded from SPECT BIE as their images were not available, therefore providing 220 subjects evaluable for efficacy (ITD) and 157 in the PP analysis.

Table 5 Subject Disposition

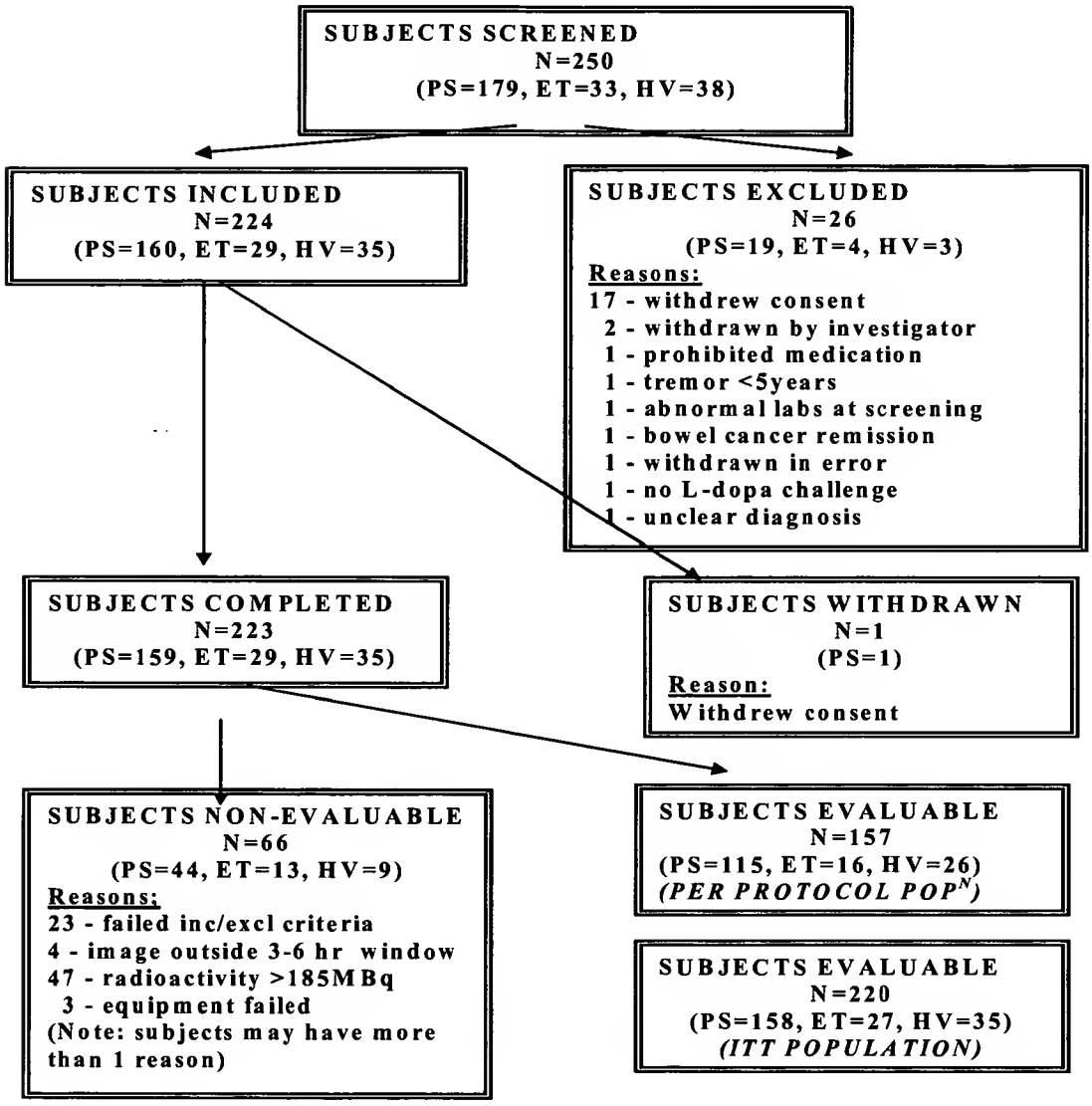
Disposition of Subjects	N
Total screened	250
Withdrawn prior to dosing	26
Withdrew consent	17
Withdrawn by investigator	2
Protocol violation[a]	7
Total dosed	224
Evaluable for safety	224
Completers	223
Non-completers	1
Withdrew consent	1
Evaluated in SPECT BIE	223
Excluded from SPECT BIE (images not available)	3
Evaluated in clinical diagnosis (SOT)	250
Excluded from clinical diagnosis	26
Evaluable for efficacy	220
Intent-to-diagnose population (ITD)	220
Per-protocol population (PP)	157

N = number of subjects for respective category; BIE = blinded image evaluation; IE = independent evaluation
ITD = Subjects who underwent SPECT imaging after receiving SPECT and underwent the standard-of-truth assessment for the relevant analysis.
Per-protocol = Subjects in the ITD population with no major protocol violations.
a. Prohibited medication, tremor <5 years, abnormal labs, bowel cancer remission, withdrawn in error, no L-DOPA challenge, unclear diagnosis.
REF: Section [14.1.1]

10.1.2 Healthy normal volunteers (European CSR)

Each of the 6 study sites provided 6 healthy volunteers (no SDD). Study site 003 (Glasgow) screened 8 volunteers with only 6 receiving test product. Of the 38 healthy volunteers screened, 35 (92.1%) were included into the study. The 3 healthy volunteers (Subjects 25, 225, and 303) excluded from the study elected to withdraw their consent. All 35 participating healthy volunteers completed the study.

Figure 4 Disposition of Patients/Healthy Volunteers (European CSR)



Included = Subject included in the study population and received test product; Excluded = Subjects excluded from the study population prior to receiving test product; Completed = Subject completed all study visits and assessments; Withdrawn = Subject did not complete all study visits and assessments or subject withdrew consent to further participation in the study; Evaluable = Fulfilled all protocol criteria for inclusion into PP analysis; Non-evaluable = Did not fulfill all protocol criteria for inclusion into PP analysis but are included in ITD analysis

10.1.3 Excluded population (European CSR)

Subjects excluded from the study population did not receive test product. Twenty-three patients and 3 volunteers were excluded for the following reasons:

- 17 elected to withdraw consent to further study participation.
- (12 PS patients - Subjects 16, 21, 23, 117, 137, 161, 184, 188, 249, 356, 357, and 359; 2 ET patients - Subjects 46 and 326 and 3 healthy volunteers - Subjects 25, 225, and 303).
- 2 PS patients were withdrawn, by the investigator, and re-screened (Subjects 155 and 251).
- 1 PS patient had an unclear diagnosis (Subject 217).
- 1 PS patient had an abnormally high GGT laboratory value at screening (Subject 10).
- 1 PS patient was withdrawn in error (Subject 309).
- 1 PS patient was not suitable in the Investigator's opinion as they were in remission for bowel cancer (Subject 310).
- 1 PS patient had no L-DOPA challenge due to hypertension (Subject 84).
- 1 ET patient took prohibited medication (Subject 17).
- 1 ET patient had tremor for less than 5 years (Subject 73).

10.1.4 Included population (European CSR)

There were 189 (90.0%) included patients from the 210 unique patients screened; 160 (84.7%) had PS and 29 (15.3%) had ET. Including the 35 healthy volunteers, the total number of included subjects was 224.

Of the 224 patients/volunteers included in the study (160 PS [SDD], 29 ET [no SDD] and 35 healthy volunteers [no SDD]), 223 completed the study. The 1 withdrawal was a PS (SDD) patient (Subject 190) who elected to withdraw consent prior to having a scan although after receiving test product.

For disposition of subjects on a center basis refer to study tables in Appendix [15.3] in the original European CSR.

10.1.5 Withdrawn population (European CSR)

One PS (SDD) patient, from the included population, withdrew consent to further study participation after receiving test product but before having an image taken (Subject 190).

10.2 Protocol Deviations

Protocol deviations are not addressed in this report. Section [10.2] of the original European CSR for this study examined protocol deviations in detail and concluded that the protocol deviations that occurred did not have an impact on the scientific value of the study results.

10.3 Demographic and Other Baseline Characteristics

10.3.1 Demographic characteristics

Subject demographics for this study are summarized in Table 6. In the overall study population, the majority of subjects were Caucasian (99%); 48% were male and 30% were female. There were a greater proportion of males in all subgroups except for healthy volunteers (43% male) and PSP (SDD) (50%). The median age for the overall study population was 63.5 years, the minimum age was 40 years, and the maximum age was 80 years. When the total population was broken down by diagnosis there were no remarkable differences in demographics between the groups with 1 exception: the minimum age for the PSP (SDD) population was 62 years.

The prevalence of PS (SDD) in the study population was 160/224 (71%) (including healthy volunteers [no SDD]) and 160/189 (85%) (excluding healthy volunteers [no SDD]).

Table 6 Summary of Subject Demographics – Safety Population

Variable	Statistic	Overall (N=224)	Diagnosis					
			Healthy Volunteer (no SDD) (N=35)	Essential Tremor (no SDD) (N=29)	Parkinson's Disease (SDD) (N=132)	MSA (SDD) (N=18)	PSP (SDD (N=10)	PS (PD, MSA, PSP) (SDD) (N=160)
Gender								
Male	n (%)	137 (61%)	15 (43%)	20 (69%)	87 (66%)	10 (56%)	5 (50%)	102 (64%)
Female	n (%)	87 (39%)	20 (57%)	9 (31%)	45 (34%)	8 (44%)	5 (50%)	58 (36%)
Race								
Caucasian	n (%)	220 (98%)	33 (94%)	29 (100%)	131 (99%)	17 (94%)	10 (100%)	158 (99%)
Black	n (%)	3 (1%)	2 (6%)	0 (0%)	0 (0%)	1 (6%)	0 (0%)	1 (1%)
Asian	n (%)	1 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (1%)
Age (yr)	n	224	35	29	132	18	10	160
	Mean (SD)	63 (9)	61 (9)	64 (9)	63 (9)	61 (8)	68 (4)	63 (9)
	Min, Max	40, 80	41, 79	46, 80	40, 80	46, 72	62, 76	40, 80
	Median	63	60	65	63	63	66	64
Height (cm)	n	214	35	28	125	16	10	151
	Mean (SD)	170 (9)	170 (8)	170 (10)	170 (8)	172 (10)	168 (10)	170 (9)
	Min, Max	147, 189	155, 185	147, 184	152, 189	156, 188	152, 182	152, 189
	Median	170	170	172	170	172	172	171
Weight (kg)	n	215	35	28	126	16	10	152
	Mean (SD)	73 (14)	74 (12)	75 (20)	72 (12)	76 (15)	70 (10)	72 (12)
	Min, Max	38.1, 130.0	53.0, 108.0	38.1, 130.0	47.0, 109.8	50.0, 100.0	54.4, 85.0	47.0, 109.8
	Median	72	73	76	71	76	71	71
BMI (kg/m^2)	n	214	35	28	125	16	10	151
	Mean (SD)	25 (4)	26 (4)	26 (6)	245 (3)	25 (4)	25 (3)	25 (3)
	Min, Max	17.6, 41.0	20.2, 37.4	17.6, 41.0	18.8, 35.0	19.9, 32.9	21.5, 30.9	18.8, 35.0
	Median	25	25	25	24	25	24	24

N = number of subjects dosed; n = number of subjects with the respective demographic information; SD = standard deviation; MSA = Multiple System Atrophy; PSP = Progressive Supranuclear Palsy; BMI = body mass index; PS = Parkinsonian syndrome. Safety population: subjects who received any amount of DaTSCAN™.
Ref: Section 14.1, Table [14.1.2].

Screening characteristics for the safety population in this study are summarized in Table 7. In the overall study population, the median systolic blood pressure was 135 mm-Hg (range 90 to 208 mm-Hg). Median diastolic blood pressure was 85 mm-Hg (range 60 to 126 mm-Hg). Median pulse rate was 72 bpm (range 48 to 100 bpm). There were no remarkable differences in demographics between the individual diagnosis groups.

Distribution of H&Y staging within the PD (SDD) population was found to be 15% (stage 1), 21% (stage 2), 13% (stage 3), and 11% (stage 4).

Table 7 Summary of Screening Characteristics – Safety Population

			Diagnosis				
Variable	**Statistic**	**Overall (N=224)**	**Healthy Volunteer (N=35)**	**Essential Tremor (N=29)**	**Parkinson's Disease (N=132)**	**MSA (N=18)**	**PSP (N=10)**
Systolic BP (mmHg)	**n**	**222**	**34**	**29**	**131**	**18**	**10**
	Mean (SD)	138 (21)	136 (19)	137 (13)	137 (22)	142 (26)	144 (17)
	Min, Max	90, 208	105, 175	110, 168	90, 205	100, 208	126, 170
	Median	135	130	139	130	141	137
Diastolic BP (mmHg)	**n**	**222**	**34**	**29**	**131**	**18**	**10**
	Mean (SD)	85 (11)	84 (9)	85 (10)	86 (11)	85 (16)	88 (12)
	Min, Max	60, 126	70, 110	68, 108	65, 126	60, 114	70, 110
	Median	85	80	84	85	85	90
Pulse Rate (bpm)	**n**	**222**	**34**	**29**	**131**	**18**	**10**
	Mean (SD)	72 (10)	65 (9)	73 (10)	73 (10)	78 (10)	73 (11)
	Min, Max	48, 100	48, 84	56, 96	56, 100	60, 92	60, 88
	Median	72	64	72	72	77	73
H&Y Stage							
1	n (%)	34 (15%)	0 (0%)	0 (0%)	34 (26%)	0 (0%)	0 (0%)
2	n (%)	46 (21%)	0 (0%)	0 (0%)	46 (35%)	0 (0%)	0 (0%)
3	n (%)	29 (13%)	0 (0%)	0 (0%)	24 (18%)	3 (17%)	2 (20%)
4	n (%)	24 (11%)	0 (0%)	0 (0%)	22 (17%)	1 (6%)	1 (10%)

N = number of subjects dosed; n = number of subjects with the respective demographic information; SD = standard deviation; MSA = Multiple System Atrophy; PSP = Progressive Supranuclear Palsy; BP=Blood pressure; H&Y= Hoehn & Yahr
Safety population: subjects who received any amount of DaTSCAN™.
Ref: Section 14.1, Table [14.1.3].

10.3.2 Investigational medicinal product and dosage received

Refer to the original European CSR for details regarding DaTSCAN™ administration (Section [12.1]). All 224 patients/healthy volunteers included into the study were injected with DaTSCAN™. The amount of radioactivity injected ranged from 111 MBq to 201 MBq. Refer to Section 9.4.4 for more details regarding the administration of DaTSCAN™.

11 EFFICACY EVALUATION

11.1 Data Sets Analyzed

Of the 250 subjects screened and evaluated in the clinical diagnosis (SOT), 224 subjects received DaTSCAN™ and 26 subjects were excluded from clinical diagnosis due to study withdrawal prior to dosing. Four of the 224 subjects were excluded from the ITD population due to unavailable SPECT BIE images (3 subjects) and consent withdrawal prior to BIE evaluation (1 subject). Of the 220 subjects included in the ITD population, 157 were included in the PP population.

11.2 Measurements of Treatment Compliance

The subjects received DaTSCAN™ under direct supervision of study personnel. Radioactivity injected was independently checked and recorded in the CRF. The vial labels, containing subject number and vial number, were attached to the subject's CRF.

11.3 Efficacy Results and Tabulations of Individual Subject Data

11.3.1 Analysis of efficacy of DaTSCAN™

Efficacy results were reported and compared for the ITD and the PP populations. Efficacy of DaTSCAN™ was determined from the BIE assessment as compared to the SOT, which, depending on the specific analysis, was either the CP diagnosis obtained at the main assessment or the CP diagnosis obtained at the 12-month follow-up. Inter-reader agreement was determined for each pair of on-site and independent SPECT readers and for each pair of independent SPECT readers.

11.3.1.1 Standard of truth and other diagnoses

(a) Standard of truth diagnosis

Although the SOT used in this study was not discussed in the original European CSR or protocol, the study used well-accepted criteria of diagnosis as selection criteria to assure that subjects had (or did not have) conditions known to be associated with striatal dopaminergic deficits. Thus the SOT was the qualifying diagnosis made prior to study entry. The SOT was used to validate the on-site visual image assessments and to determine sensitivity and specificity of the on-site SPECT and BIE reads.

11.3.1.2 Primary analysis

(a) Efficacy of On-Site DaTSCAN™ SPECT Read

Data on the sensitivity and specificity of the on-site visual image reads for detecting or excluding a SDD are presented in Table 8 for the ITD population and in Table 9 for the PP population. Results were similar for both populations.

Comparison of the original results in the European CSR (Sections [11.4.1.1] and [11.4.1.2]) with the results reported here showed that, with the exception of the ITD specificity (which was slightly lower currently (98.4%) than originally (100%)), all results were the same for both populations.

Table 8 Efficacy of On-Site DaTSCAN™ SPECT Read (ITD Population)

On-Site DaTSCAN™ Image Visual Assessment	Clinical Diagnosis (Standard of Truth) PS (SDD Present) n (%)	Non-PS (SDD Absent) n (%)	Total n (%)
Abnormal (SDD Present)	154 (70%)	1 (0%)	155 (70%)
Normal (SDD Absent)	4 (2%)	61 (28%)	65 (30%)
Total	158 (72%)	62 (28%)	220

Analysis Summary	Statistic	
Sensitivity	95% CI[a]	97.5% (93.6, 99.3)
Specificity	95% CI[a]	98.4% (91.3, 100.0)

n = number of subjects in each category; PS = Parkinsonian syndrome; SDD= striatal dopaminergic deficits.
Percentage based on the number of subjects with both evaluations.
a. CI = exact 95%, 2-sided.
REF: Section 14.2, Table [14.2.1.1]

Table 9 Efficacy of On-Site DaTSCAN™ SPECT Read PP Population

On-Site DaTSCAN™ Image Visual Assessment	Clinical Diagnosis (Standard of Truth) PS (SDD Present) n (%)	Non-PS (SDD Absent) n (%)	Total n (%)
Abnormal (SDD Present)	111 (71%)	0 (0%)	111 (71%)
Normal (SDD Absent)	4 (3%)	42 (27%)	46 (29%)
Total	115 (73%)	42 (27%)	157

Analysis Summary	Statistic	
Sensitivity	95% CI[a]	96.5% (91.3, 99.0)
Specificity	95% CI[a]	100.0% (91.6, 100.0)

n = number of subjects in each category; PS = Parkinsonian syndrome; SDD= striatal dopaminergic deficits.
Percentage based on the number of subjects with both evaluations.
a. CI = exact 95%, 2-sided.
REF: Section 14.2, Table [14.2.1.2]

(b) Efficacy of On-Site DaTSCAN™ SPECT: Other Secondary Parameters (European CSR)

(i) Per-Protocol and ITD- Effect of Center

Refer to the original European CSR for details regarding results found in Summary Tables [3] and [7]. The effect of center on the binary response of abnormal/normal striatal uptake was assessed for PS (SDD) and ET (no SDD) patients using Fisher's exact test. For the PS (SDD) group in the PP population, there was no evidence of a relationship between centers and institutional reads ($p = 0.327$).

For the ITD population, in the PS (SDD) group the p-value of 0.456 provided no evidence of a relationship between centers and institutional reads.

(ii) Per-Protocol and ITD- Effect of Age

Refer to the original European CSR for details regarding results found in Summary Tables [4] and [8]. The effect of the age group on the binary response of abnormal/normal striatal uptake was assessed for PS (SDD) and ET (no SDD) patients using the Wilcoxon two-sample test. For the PS (SDD) group in the PP population, the p-value of 0.942 provided no evidence of a difference in the pattern of age groups between abnormal and normal institutional reads.

For the ITD population, in the PS (SDD) group the p-value of 0.838 provided no evidence of a difference in the pattern of age groups between abnormal and normal institutional reads.

11.3.1.3 Secondary analysis

(a) Efficacy of "Consensus" (Majority) SPECT BIE Assessment

A Blinded Read panel consisting of 5 of the 13 investigators involved in the study was selected and each panel member was required to evaluate all the blinded images, independent of other panel members, at his/her own clinical facility. Evaluation of each blinded image was based on a visual assessment of uptake of DaTSCAN™ Injection in the striatum in accordance with the following classifications:

(1) Normal DaTSCAN™ SPECT images;

(2) Abnormal DaTSCAN™ SPECT image type 1;

(3) Abnormal DaTSCAN™ SPECT image type 2;

(4) Abnormal DaTSCAN™ SPECT image type 3.

The clinical diagnosis was performed prior to DaTSCAN™ imaging and the BIE. These data are presented in Table 10 for the ITD population and in Table 11 for the PP population. Results were similar for both populations. The BIE assessment was compared to the clinical diagnosis and classified as TP, TN, FP, or FN, and sensitivity and specificity were determined.

The sensitivity and specificity of the BIE majority ("consensus") assessment for detecting or excluding a SDD were 94.9% and 93.5%, respectively in the ITD population, and 94.8% and 92.9% respectively in the PP population.

Comparison of the original results in the European CSR (Sections [11.4.2.1] and [11.4.2.2]) with the results reported here showed that the ITD and PP sensitivity were the same in both reports, but the specificity was slightly different. Specificity was slightly higher currently (93.5%) than originally (92.6%) in the ITD population and slightly lower currently (92.9%) than originally (93.8%) in the PP population. These small differences are not considered to be clinically significant.

Table 10 Efficacy of "Consensus" (Majority) SPECT BIE Assessment – ITD Population

"Consensus" (majority) DaTSCAN™ Blinded Image Assessment t	Clinical Diagnosis (Standard of Truth) PS (SDD Present) n (%)	Non-PS (SDD Absent) n (%)	Total n (%)
Abnormal (SDD Present)	150 (68%)	4 (2%)	154 (70%)
Normal (SDD Absent)	8 (4%)	58 (26%)	66 (30%)
Total	158 (72%)	62 (28%)	220

Analysis Summary	Statistic	
Sensitivity	95% CI [a]	94.9% (90.3, 97.8)
Specificity	95% CI [a]	93.5% (84.3, 98.2)

n = number of subjects in each category; PS = Parkinsonian syndrome; SDD= striatal dopaminergic deficits.
Percentage based on the number of subjects with both evaluations.
a. CI = exact 95%, 2-sided.
REF: Section 14.2, Table [14.2.2.1]

Table 11 Efficacy of "Consensus" (Majority) SPECT BIE – PP Population

Consensus (majority) DaTSCAN™ Blinded Image Assessment	Clinical Diagnosis (Standard of Truth) PS (SDD Present) n (%)	Non-PS (SDD Absent) n (%)	Total n (%)
Abnormal (SDD Present)	109 (69%)	3 (2%)	112 (71%)
Normal (SDD Absent)	6(4%)	39 (25%)	45 (29%)
Total	115 (73%)	42 (27%)	157

Analysis Summary	Statistic	
Sensitivity	95% CI [a]	94.8% (89.0, 98.1)
Specificity	95% CI [a]	92.9% (80.5, 98.5)

n = number of subjects in each category; PS = Parkinsonian syndrome; SDD= striatal dopaminergic deficits.
Percentage based on the number of subjects with both evaluations.
a. CI = exact 95%, 2-sided.
REF: Section 14.2, Table [14.2.2.2]

(b) SPECT BIE Assessment and the Clinical Diagnosis by Reader

By-reader results are presented in Table 12 for the ITD population and in Table 13 for the PP population. For each reader, sensitivity and specificity were consistent in both populations. Sensitivity among the readers ranged from 92.4% to 96.8% and 92.2% to 97.4% in the ITD and PP populations, respectively. Specificity ranged from 80.6% to 96.8% and 85.7% to 97.6% in the ITD and PP populations, respectively. Comparison of the original results in the European CSR (Sections [11.4.1.1] and [11.4.1.2]) with the results reported here shows that the range of sensitivity is the same for the ITD population, but is increased somewhat in the PP population reported here (80.6% to 96.8%) compared with the original EU results (74.1% to 96.3%).

Table 12 Efficacy of SPECT BIE by Reader – ITD Population

		Clinical Diagnosis (Standard of Truth)		
		PS (SDD Present)	Non-PS (SDD Absent)	Total
Parameter	Statistic	n (%)	n (%)	n (%)
Reader A				
Abnormal (PS, SDD Present)		147 (67%)	4 (2%)	151 (69%)
Normal (Non-PS, SDD Absent)		11 (5%)	58 (26%)	69 (31%)
Total		158 (72%)	62 (28%)	220
Sensitivity	% (95% CI)[a]	93.0% (87.9, 96.5)		
Specificity	% (95% CI)[a]	93.5% (84.3, 98.2)		
Reader B				
Abnormal (PS, SDD Present)		153 (70%)	12 (5%)	165 (75%)
Normal (Non-PS, SDD Absent)		5 (2%)	50 (23%)	55 (25%)
Total		158 (72%)	62 (28%)	220
Sensitivity	% (95% CI)[a]	96.8% (92.8, 99.0)		
Specificity	% (95% CI)[a]	80.6% (68.6, 89.6)		
Reader C				
Abnormal (PS, SDD Present)		152 (69%)	5 (2%)	157 (71%)
Normal (Non-PS, SDD Absent)		6 (3%)	57 (26%)	63 (29%)
Total		158 (72%)	62 (28%)	220
Sensitivity	% (95% CI)[a]	96.2% (91.9, 98.6)		
Specificity	% (95% CI)[a]	91.9% (82.2, 97.3)		
Reader D				
Abnormal (PS, SDD Present)		146 (66%)	2 (1%)	148 (67%)
Normal (Non-PS, SDD Absent)		12 (5%)	60 (27%)	72 (33%)
Total		158 (72%)	62 (28%)	220
Sensitivity	% (95% CI)[a]	92.4% (87.1, 96.0)		
Specificity	% (95% CI)[a]	96.8% (88.8, 99.6)		
Reader E				
Abnormal (PS, SDD Present)		149 (68%)	5 (2%)	154 (70%)
Normal (Non-PS, SDD Absent)		9 (4%)	57 (26%)	66 (30%)
Majority		158 (72%)	62 (28%)	220
Sensitivity	% (95% CI)[a]	94.3% (89.5, 97.4)		
Specificity	% (95% CI)[a]	91.9% (82.2, 97.3)		

n = number of subjects in each category; PS = Parkinsonian syndrome; BIE = blinded image evaluation; SDD = striatal dopaminergic deficits.
Percentage based on the number of subjects with both evaluations.
[a]CI = exact (95%; 2-sided).
REF: Section 14.2, Table [14.2.3.1]

Table 13 Efficacy of SPECT BIE by Reader – PP Population

Parameter	Statistic	Clinical Diagnosis (Standard of Truth) PS (SDD Present) n (%)	Non-PS (SDD Absent) n (%)	Total n (%)
Reader A				
Abnormal (PS, SDD Present)		106 (68%)	3 (2%)	109 (69%)
Normal (Non-PS, SDD Absent)		9 (6%)	39 (25%)	48 (31%)
Total		115 (73%)	42 (27%)	157
Sensitivity	% (95% CI)[a]	92.2% (85.7, 96.4)		
Specificity	% (95% CI)[a]	92.9% (80.5, 98.5)		
Reader B				
Abnormal (PS, SDD Present)		112 (71%)	6 (4%)	118 (75%)
Normal (Non-PS, SDD Absent)		3 (2%)	36 (23%)	39 (25%)
Total		115 (73%)	42 (27%)	157
Sensitivity	% (95% CI)[a]	97.4% (92.6, 99.5)		
Specificity	% (95% CI)[a]	85.7% (71.5, 94.6)		
Reader C				
Abnormal (PS, SDD Present)		111 (71%)	2 (1%)	113 (72%)
Normal (Non-PS, SDD Absent)		4 (3%)	40 (25%)	44 (28%)
Total		115 (73%)	42 (27%)	157
Sensitivity	% (95% CI)[a]	96.5% (91.3, 99.0)		
Specificity	% (95% CI)[a]	95.2% (83.8, 99.4)		
Reader D				
Abnormal (PS, SDD Present)		106 (68%)	1 (1%)	107 (68%)
Normal (Non-PS, SDD Absent)		9 (6%)	41 (26%)	50 (32%)
Total		115 (73%)	42 (27%)	157
Sensitivity	% (95% CI)a	92.2% (85.7, 96.4)		
Specificity	% (95% CI)a	97.6% (87.4, 99.9)		
Reader E				
Abnormal (PS, SDD Present)		108 (69%)	4 (3%)	112 (71%)
Normal (Non-PS, SDD Absent)		7 (4%)	38 (24%)	45 (29%)
Majority		115 (73%)	42 (27%)	157
Sensitivity	% (95% CI)a	93.9% (87.9, 97.5)		
Specificity	% (95% CI)a	90.5% (77.4, 97.3)		

n = number of subjects in each category; PS = Parkinsonian syndrome; BIE = blinded image evaluation; SDD= striatal dopaminergic deficits.
Percentage based on the number of subjects with both evaluations.
[a]CI = exact (95%; 2-sided).
REF: Section 14.2, Table [14.2.3.2]

(c) Inter-Reader Agreement for BIE SPECT Visual Assessment

Inter-reader SPECT assessment analyses performed in this study were not discussed in the original European study CSR or protocol, but are discussed here in the US report. Inter-reader agreement data are presented in Table 14.

Agreement between the 5 BIE readers was excellent, with Cohen's κ values ranging from 0.83 to 0.92; the pooled coefficient for all 5 readers was 0.87. Agreement between the BIE readers and the on-site reads was similar, with Cohen's κ ranging from 0.88 to 0.94.

Table 14 Inter-Reader Agreement Between Each Pair of On-site and Independent SPECT Readers in Visual Assessment of DaTSCAN™ SPECT Images

Reader	Compare Reader	N	n	Cohen's Kappa k (95% CI)
A	Reader B	157	148	0.86 (0.77, 0.95)
A	Reader C	157	149	0.88 (0.79, 0.96)
A	Reader D	157	147	0.85 (0.76, 0.94)
A	Reader E	157	152	0.92 (0.86, 0.99)
B	Reader C	157	150	0.89 (0.80, 0.97)
B	Reader D	157	146	0.83 (0.73, 0.92)
B	Reader E	157	147	0.84 (0.74, 0.93)
C	Reader D	157	151	0.91 (0.84, 0.98)
C	Reader E	157	150	0.89 (0.81, 0.97)
D	Reader E	157	148	0.86 (0.78, 0.95)
Readers A, B, C, D, E[a]		157	139	0.87 (0.82, 0.92)
A	On-site	157	149	0.88 (0.80, 0.96)
B	On-site	157	150	0.89 (0.81, 0.97)
C	On-site	157	153	0.94 (0.88, 1.00)
D	On-site	157	151	0.91 (0.84, 0.98)
E	On-site	157	150	0.89 (0.81, 0.97)

N = Number of images with non-missing value for DaTSCAN™ SPECT visual assessment for the 2 respective readers; for the generalized kappa: number of images with non-missing values for all 5 readers; n = number of images with agreement
a. Multiple coefficient for all 5 independent SPECT readers.
REF: Section 14.2, Table [14.2.6]

(d) Efficacy of "Consensus" (Majority) SPECT BIE by H&Y score

Efficacy data stratified by H&Y score are presented in Table 15 for the ITD population and in Table 16 for the PP population. For the 137 PS (SDD) subjects in the ITD population, there was no evidence of a significant difference in sensitivity for onsite DaTSCAN™ SPECT or "consensus" (majority) BIE assessments (p>0.999 and p=0.869, respectively). Sensitivity by H&Y disease stage ranged from 96.7% to 100.0% for on-site read and 94.3% to 100.0% for BIE read.

Similarly for the PP population, there was no evidence of a significant difference in sensitivity for onsite DaTSCAN™ SPECT or "consensus" (majority) BIE assessments (p=0.785 and p=0.831, respectively). Sensitivity by H&Y disease stage ranged from 94.4% to 100.0% for on-site read and BIE read respectively.

Comparison of original results in the European CSR (Sections [11.4.1.1] and [11.4.1.2]) with the results reported here shows that sensitivity ranged slightly to somewhat higher currently for both the on-site/institutional reads in the ITD and PP populations (96.7% to 100% and 94.4% to 100%, respectively) than originally (96.0% to 100% and 92.9% and 100%, respectively); all "consensus" (majority) BIE result ranges were the same for both populations in each report.

Table 15 Sensitivity of On-Site DaTSCAN™ SPECT Read and "Consensus" (Majority) BIE Read Response Rates by H&Y Disease Stage for PS Subjects – ITD Population

Parameter	H&Y Assessment	N	Read Result: Abnormal (SDD Present)	Read Result: Normal (SDD Absent)	Sensitivity[a] (95% CI)[b]	p-value[c]
On-Site DaTSCAN™ SPECT Read	1	35	34	1	97.1% (85.1, 99.9)	>0.999
	2	48	47	1	97.9% (88.9, 99.9)	
	3	30	29	1	96.7% (82.8, 99.9)	
	4	24	24	0	100.0% (85.8, 100.0)	
"Consensus" (Majority) BIE Read	1	35	33	2	94.3% (80.8, 99.3)	0.869
	2	48	46	2	95.8% (85.7, 99.5)	
	3	30	29	1	96.7% (82.8, 99.9)	
	4	24	24	0	100.0% (85.8, 100.0)	

BIE = blinded image evaluation
N = number of subjects in each category; PS = Parkinsonian syndrome; SDD= striatal dopaminergic deficits; H&Y= Hoehn & Yahr.
Response rate based on the number of subjects with abnormal evaluations.
a. Clinical diagnosis used as standard of truth.
b. CI = exact (95%; 2-sided).
c. p-value = 2-sided Fisher's exact test.
REF: Section 14.2, Table [14.2.4.1]

Table 16 Sensitivity of On-Site DaTSCAN™ SPECT Read and "Consensus" (Majority) BIE Read Response Rates by H&Y Disease Stage for PS Subjects – PP Population

Parameter	H&Y Assessment	N	Read Result: Abnormal (SDD Present)	Read Result: Normal (SDD Absent)	Sensitivity[a] (95% CI)[b]	p-value[c]
On-Site DaTSCAN™ SPECT Read	1	23	22	1	95.7% (78.1, 99.9)	0.785
	2	38	37	1	97.4% (86.2, 99.9)	
	3	18	17	1	94.4% (72.7, 99.9)	
	4	20	20	0	100.0% (83.2, 100.0)	
"Consensus" (Majority) BIE Read	1	23	22	1	95.7% (78.1, 99.9)	0.831
	2	38	36	2	94.7% (82.3, 99.4)	
	3	18	17	1	94.4% (72.7, 99.9)	
	4	20	20	0	100.0% (83.2, 100.0)	

BIE = blinded image evaluation
N = number of subjects in each category; PS = Parkinsonian syndrome; SDD= striatal dopaminergic deficits; H&Y= Hoehn & Yahr.
Response rate based on the number of subjects with abnormal evaluations.
[a]Clinical diagnosis used as standard of truth.
[b]CI = exact (95%; 2-sided).
[c]p-value = 2-sided Fisher's exact test.
REF: Section 14.2, Table [14.2.4.2]

(e) Efficacy of "Consensus" (Majority) SPECT BIE by UPDRS Score

Although UPDRS assessment analyses performed in this study were not discussed in the original European CSR or protocol, the UPDRS is a well-accepted and frequently used assessment in PD (SDD) studies and is therefore included in the US submission. Efficacy data are presented by UPDRS category in Table 17 for the ITD population and in Table 18 for the PP population. For the 137 PS (SDD) subjects in the ITD population, there was no evidence of a significant difference in sensitivity for onsite DaTSCAN™ SPECT or "consensus" (majority) BIE assessments ($p>0.999$ and $p=0.869$, respectively). Sensitivity by UPDRS screening scores (<22 or ≥22) were 98.6% and 97.1%, respectively for on-site read and 97.1% and 95.6%, respectively, for BIE read.

Similarly for the PP population, there was no evidence of a significant difference in sensitivity for onsite DaTSCAN™ SPECT or "consensus" (majority) BIE assessments ($p=0.785$ and $p=0.831$, respectively). Sensitivity by UPDRS screening scores (<22 or ≥22) were 97.8% and 96.2%, respectively for on-site read and 97.8% and 94.3%, respectively, for BIE read.

Table 17 Sensitivity of On-Site DaTSCAN™ SPECT Read and "Consensus" (Majority) BIE Read Response Rates by Screening UPDRS Score Category for PS Subjects – ITD Population

Parameter	Screening UPDRS	N	Read Result: Abnormal (SDD Present)	Read Result: Normal (SDD Absent)	Response Rate (Sensitivity)[a] (95% CI)[b]	p-value[c]
On-Site DaTSCAN™ SPECT Read	<22	69	68	1	98.6% (92.2, 100.0)	0.619
	≥22	68	66	2	97.1% (89.8, 99.6)	
"Consensus" (Majority) BIE Read	<22	69	67	2	97.1% (89.9, 99.6)	0.681
	≥22	68	65	3	95.6% (87.6, 99.1)	

BIE = blinded image evaluation
N = number of subjects in each category; PS = Parkinsonian syndrome; SDD = striatal dopaminergic deficits; UPDRS = Unified Parkinson's disease rating scale.
Response rate based on the number of subjects with abnormal evaluations.
[a]Clinical diagnosis used as standard of truth.
[b]CI = exact (95%; 2-sided).
[c]p-value = 2-sided Fisher's exact test.
REF: Section 14.2, Table [14.2.5.1]

Table 18 Sensitivity of On-Site DaTSCAN™ SPECT Read and "Consensus" (Majority) BIE Read Response Rates by Screening UPDRS Score Category for PS Subjects – PP Population

Parameter	Screening UPDRS	N	Read Result: Abnormal (SDD Present)	Read Result: Normal (SDD Absent)	Response Rate (Sensitivity)[a] (95% CI)[b]	p-value[c]
On-Site DaTSCAN™ SPECT Read	<22	46	45	1	97.8% (88.5, 99.9)	>0.999
	≥22	53	51	2	96.2% (87.0, 99.5)	
"Consensus" (Majority) BIE Read	<22	46	45	1	97.8% (88.5, 99.9)	0.621
	≥22	53	50	3	94.3% (84.3, 98.8)	

BIE = blinded image evaluation
N = number of subjects in each category; PS = Parkinsonian syndrome; SDD = striatal dopaminergic deficits; UPDRS = Unified Parkinson's disease rating scale.
Response rate based on the number of subjects with abnormal evaluations.
[a]Clinical diagnosis used as standard of truth.
[b]CI = exact (95%; 2-sided).
[c]p-value = 2-sided Fisher's exact test.
REF: Section 14.2, Table [14.2.5.2]

(f) Other "Consensus" (Majority) BIE Assessments — European CSR

(i) Per-protocol and ITD - Effect of Center

Refer to the original European CSR for details (Summary Tables [11] and [17]). The effect of center on the binary response of abnormal/normal striatal uptake was assessed for PS (SDD) and ET (no SDD) patients using Fisher's exact test. For the PS (SDD) group in the PP population, the p-value of 0.060 was approaching statistical significance. Further investigation showed the response rates were similar across 5 of the 6 centers; for the Gent center though, a lower response rate was observed 60.0% (3/5) — refer to Section [11.4.2.1] of the original European study for further details.

For the PS (SDD) group in the ITD population, the p-value of 0.227 provided no evidence of a relationship between centre and "consensus" (majority) Blinded Reads. For the ET (no SDD) group the p-value of 0.182 provided no evidence of a relationship between centre and "consensus" (majority) Blinded Reads.

(ii) Per-protocol and ITD - Effect of Age

Please consult the original European CSR (Summary Tables [12] and [18]). The effect of the age group on the binary response of abnormal/normal striatal uptake was assessed for PS (SDD) and ET (no SDD) patients using the Wilcoxon two-sample test. For the PS (SDD) group in the PP population, the p-value of 0.774 provided no evidence of a difference in the pattern of age groups between abnormal and normal "consensus" (majority) Blinded Reads. For the ET (no SDD) group the p-value of 0.723 provided no evidence of a difference in the pattern of age groups between abnormal and normal "consensus" (majority) Blinded Reads.

For the PS (SDD) group in the ITD population, the p-value of 0.930 provided no evidence of a difference in the pattern of age groups between abnormal and normal "consensus" (majority) Blinded Reads. For the ET (no SDD) group the p-value of 0.884 provided no evidence of a difference in the pattern of age groups between abnormal and normal "consensus" (majority) Blinded Reads.

(g) Semi-Quantitative Analyses (European CSR)

The original European CSR contains details regarding the following additional study parameters. Tables [15.3.30] to [15.3.37] summarize specific uptake, ratio of specific to non-specific uptake, asymmetry index and ratio of putamen/caudate specific uptake for ITD and PP patient/healthy volunteers. Statistical Outputs [15.4.21] to [15.4.28] summarize specific uptake, ratio of specific to non-specific uptake, asymmetry index and ratio of putamen/caudate specific uptake for ITD and PP patients/healthy volunteers, respectively.

The results for each of the 4 semi-quantitative assessments were clear and consistent for both ITD and PP patient/volunteers respectively; all analyses showed no differences between the ET (no SDD) and healthy volunteer (no SDD) groups but a highly significant difference between these groups and the PS (SDD) group ($p = <0.001$). Specific uptake, ratio of specific to non-specific uptake and ratio of putamen/caudate specific uptake were all greater for the ET (no SDD) and healthy volunteer (no SDD) groups than for the PS (SDD) group, while asymmetry index was smaller for the ET (no SDD) and healthy volunteer (no SDD) groups than for the PS (SDD) group. The differences between study populations were not dependent upon ROI or side of onset. The results held for both the ITD and the PP data sets. Summary Tables [21] to [28] of the original European CSR presented the key analysis of variance results outlining the least squares mean for each of the 3 study populations, each of the 3 study population differences with 95% CLs, and the p-value for the overall treatment effect. The semi-quantitative results are consistent with a reduced number of dopaminergic nigrostriatal neurons in the PS subjects, which is consistent with the known loss of these neurons in PS. Such loss does not occur in ET or in healthy subjects.

(h) Statistical Interactions

On completion of the semi-quantitative analyses it became apparent that a number of statistical interactions were identified. These were center by patient/volunteer group interactions in the ITD analyses, specifically with regard to; specific uptake; ratio of specific to non- specific uptake and putamen-caudate ratio of uptake (Table 19). These interactions are further summarized in Section [11.5] (Summary Table [29]) of the original European CSR.

Table 19 Statistically Significant Interactions for ITD Population (Center by Patient/Volunteer)

Assessment	ROI	Side	p-Value[a]
Specific Uptake	Striatum	Left	0.007
		Right	0.007
	Caudate	Left	0.044
	Putamen	Left	0.002*
		Right	0.001
Specific to Non-specific Uptake	Striatum	Left	0.025*
	Putamen	Left	0.001*
		Right	0.009*
Putamen to Caudate Uptake	Putamen/ Caudate	Left	0.019
		Right	0.001

a - ANOVA F-test
* - Also statistically significant for PP population

These interactions were investigated further by producing summary tables of the semi-quantitative data by centre and patient/healthy volunteer group. In all cases differences between the ET (no SDD) versus PS (SDD) and healthy volunteer (no SDD) versus PS (SDD) groups for each of the centers were in the same direction, but there were variations in the magnitude of these differences. Differences between the patient/volunteer groups (ET (no SDD) versus PS [SDD] and healthy volunteers (no SDD) versus [PS]) with respect to specific uptake were 2 to 3 times larger in the Munich and Glasgow centers than the other centers. Similarly, for the ratio of specific to non-specific uptake, the Glasgow centre produced differences up to twice the magnitude of the other centers, and for the putamen-caudate ratio, differences were much smaller in the Marburg and Gent centers than in the others.

Another possible explanation for the presence of these interactions that was explored was the inclusion of the healthy volunteers in the analysis. An exploratory analysis was performed, removing the healthy volunteers and a number (approximately a third) of the interactions were no longer found to be significant.

As the interactions were primarily due to variations in magnitude (without a change in direction) and the analysis was secondary and exploratory in nature, the planned analysis removing the interaction term from the model was still performed. All preceding semi-quantitative results are based on this analysis but some care should be taken with their interpretation due to these interactions.

11.4 Efficacy Conclusions

- The revised primary objective of this study was to determine the sensitivity and specificity of visual assessments of DaTSCAN™ images for detecting or excluding SDD in subjects with movement disorders (PS [PD, MSA, or PSP; all SDD related] or ET [no SDD]. Subjects with PS are known to have striatal dopaminergic deficits based on the known pathophysiology of this syndrome, and subjects without PS (e.g. those

with ET [no SDD] and the healthy volunteers [no SDD]) are known not to have striatal dopaminergic deficits. Although the SOT used in this study was not discussed in the original European CSR or protocol, the study used well-accepted criteria of diagnosis as selection criteria to assure that subjects had (or did not have) conditions known to be associated with striatal dopaminergic deficits. These diagnoses served as the SOT to permit validation of the DaTSCAN™ image assessments, and they were performed before DaTSCAN™ imaging.

- The visual assessment of DaTSCAN™ striatal uptake by the on-site SPECT assessment represented the primary efficacy endpoint for the study. This showed high sensitivity (97.5%) and specificity (98.4%) in detecting or excluding SDD, which, in the study population (those with symptoms of movement disorders) allowed differentiation between PS (SDD) and non-PS (ET; no SDD) subjects, respectively. PP results were similar. The "consensus" (majority) BIE assessments also gave similar results for ITD analyses with a sensitivity (94.9%) and specificity (93.5%). PP results were again similar. The consistency of the on-site and blinded reads indicates that the visual image assessment of DaTSCAN is straightforward and little affected by clinical information that the on-site readers may have had.

- By-reader BIE sensitivity and specificity percentages were consistent in both the ITD and PP populations. In the ITD population, by-reader sensitivity ranged from 92.4% to 96.8% and specificity ranged from 80.6% to 96.8%.

- Inter-reader agreement between the 5 SPECT BIE readers was excellent, with Cohen's κ values ranging from 0.83 to 0.92; the pooled coefficient for all 5 readers was 0.87. Agreement between the BIE readers compared with the on-site readers showed that the on-site reader agreement was higher, with Cohen's κ values ranging from 0.88 to 0.94.

- Sensitivity did not vary by H&Y or UPDRS score.

- The results reported here show that DaTSCAN™ was able to detect or exclude a SDD with high sensitivity and specificity.

Additional secondary endpoints were not analyzed for this report but were included in the European CSR. In brief:

- For the PS (SDD) group in the ITD and PP populations, there was no evidence of a relationship between centers and institutional reads ($p=0.838$ and $p=0.942$, respectively). This was also true for "consensus" (majority) Blinded reads for both study populations.

- For the PS (SDD) group in the ITD and PP populations, there was no evidence of a significant difference in age group patterns for institutional reads ($p=0.774$ and $p=0.930$) This was also true for "consensus" (majority) Blinded reads for both study populations.

- The results for each of the 4 semi-quantitative assessments were clear and consistent for both ITD and PP patient/volunteers respectively; all analyses showed no differences between the ET (no SDD) and healthy volunteer (no SDD) groups but a highly significant difference between these groups and the PS (SDD) group ($p = <0.001$). Specific uptake, ratio of specific to non-specific uptake and ratio of putamen/caudate specific uptake were all greater for the ET (no SDD) and healthy volunteer (no SDD) groups than for the PS (SDD) group, while asymmetry index was smaller for the ET (no SDD) and healthy volunteer (no SDD) groups than for the PS (SDD) group. The differences between study populations were not dependent upon ROI or side of onset. The results held for both the ITD and the PP data sets. The semi-quantitative results are consistent with a reduced number of dopaminergic nigrostriatal neurons in the PS subjects, which is consistent with the known loss of these neurons in PS. Such loss does not occur in ET or in healthy subjects.

12 SAFETY EVALUATION

The safety analysis performed for this report addresses AEs, SAEs, and deaths. Other safety parameters that were part of the study (hematology, vital signs, ECG, and physical examination) were analyzed and presented in the original European CSR for this study and are summarized briefly in this report.

12.1 Adverse Events

12.1.1 Brief summary of adverse events

Of the 224 subjects included in the safety population, 36 (16%) had a total of 69 AEs; of these, 15 subjects (7%) had AEs that were considered related to study drug, and only 2 AEs in 2 subjects were severe (PD and headache). There were no deaths or study discontinuations due to AEs during the course of this study. One subject experienced an SAE (exacerbation of PD) that was considered unrelated to the study drug. An overview of AEs occurring during this study is presented in Table 20. In the original European CSR, it was reported that a total of 65 events were experienced by 36 subjects, as well as that a total of 30 related events were experienced by 15 subjects. As evident from Table 20, these event totals have changed as the results in the European study did not count each incidence of the same event as a new event when it occurred in the same subject.

Table 20 Overall Summary of Adverse Events – Safety Population

	All Events (N=224) n (%)	Study Drug Related n (%)
Subjects with at least 1 AE	36 (16%)	15 (7%)
Number of AEs	69	32
Maximum Intensity[a]		
Mild	14 (6%)	5 (2%)
Moderate	20 (9%)	9 (4%)
Severe	2 (<1%)	1 (<1%)
Subjects with at least 1 SAE	1 (<1%)	0 (0%)
Subjects with at least 1 AE leading to discontinuation	0 (0%)	0 (0%)
Deaths	0 (0%)	0 (0%)

N = number of subjects in the safety population; n = number of subjects in each category; AE = adverse event; SAE = serious adverse event.
Subjects with more than 1 occurrence in a category are counted once. Percentages are based on N.
a. Maximum AE severity for each subject is used for tabulation.
REF: Section 4.2, Table [14.3.1.1]

12.1.2 Display of adverse events

A summary of AEs by system organ class (SOC), preferred term and relationship can be found in Section 14.3, Table [14.3.1.2], and a summary of AEs by SOC, preferred term, and intensity can be found in Section 14.3, Table [14.3.1.3].

12.1.3 Analysis of adverse events

The most common AEs were headache, experienced by 10 subjects (4%) and nasopharyngitis (6 subjects, 3%). All other AEs were experienced by 1% or less than 1% of subjects. Of the 10 subjects (4%) who experienced headache, 7 cases (3%) were considered study-drug related. Vertigo, hunger and formication (paresthesia) were experienced by 3 subjects each and all were considered study-drug related. All other related AEs were experienced by only 1 subject each and included the following: anemia, dry mouth, nausea, asthenia, chest pain, injection site warmth, vessel puncture site hematoma, hypoalbuminemia, akinesia, balance disorder, dizziness, hemicephalalgia, hematuria, proteinuria, and cough. One subject's related AE of headache was also considered to be severe. The only other severe event of PD (SDD) was considered unrelated to study drug.

The AE profile was reviewed to look for any of the known effects of cocaine. The known effects of cocaine are nervousness, restlessness, excitement, euphoria, hallucinations, tachypnea, bradycardia at low doses, tachycardia at moderate doses, hypertension, vomiting due to CNS stimulation, tremors, and seizures [McEvoy, 2005]. One of the 224 subjects (0.4%) had an AE that is a known side effect of cocaine: 1 subject had tremor which was considered unrelated to DaTSCAN™ by the investigator.

12.1.4 Listing of adverse events by subject

A listing of all AEs by subject was not produced for this report. A listing of SAEs by subject can be found in Section 14.3, Table [14.3.2.2].

12.2 Deaths and Other Serious or Significant Adverse Events

12.2.1 Deaths

No deaths occurred during this study.

12.2.2 Other serious adverse events

One subject, Subject 003-0081, experienced a SAE of PD (preferred term) on the second day following DaTSCAN™ administration. The verbatim term was exacerbation of PD. The intensity was severe and the event was considered not related to study drug. The subject recovered 11 days later and the SAE was considered resolved.

12.2.3 Other significant adverse events

There were no other significant AEs during this study.

12.2.4 Analysis and discussion of deaths, other serious adverse events and other significant adverse events

The 1 SAE that occurred during this study resolved and was not considered related to study drug.

12.3 Clinical Laboratory Evaluation

Clinical laboratory evaluations (serum biochemistry, hematology, and urinalysis) are not addressed in this report but were presented in Section [12.3] of the original European CSR. The results revealed no apparent safety signals for DaTSCAN™.

12.4 Vital Signs

Vital signs are not addressed in this report but were presented in Section [12.4] of the original European CSR. The results revealed no apparent safety signals for DaTSCAN™.

12.5 Electrocardiograms

The results of ECGs are not addressed in this report but were presented in Section [12.5] of the original European CSR. Twelve-lead ECG assessments were performed at screening and follow-up. The results revealed no apparent safety signal for DaTSCAN™.

12.6 Physical Examination

Physical examinations are not addressed in this report. Table [15.2.16] of the original European CSR for this study detailed physical examination results examined and no findings were addressed in the report, indicating that these findings did not have an impact on the scientific value of the study results.

12.7 Safety Conclusions

- Among the 224 subjects in the safety population, 36 subjects (16%) experienced a total of 69 AEs and only 2 AEs were severe (PD (1 subject) and headache (1 subject). Fifteen subjects (7%) experienced 32 AEs that were considered related to DaTSCAN™; the most common related AEs were headache (7 subjects) and vertigo, hunger, and formication (paresthesia) (3 subjects each).

- One SAE of PD exacerbation was reported but was not deemed to be related to DaTSCAN™.
- Other than 1 case of tremor, there were no AEs suggestive of cocaine like effects. This is consistent with the low mass dose of [^{123}I]FP-CIT.
- No safety concerns were noted in the results for clinical laboratory tests, vital signs, or ECG. These study results indicate DaTSCAN™ to be a safe and well-tolerated radiopharmaceutical.

13 DISCUSSION AND OVERALL CONCLUSIONS

13.1 Efficacy Discussion

DaTSCAN™ [Ioflupane (^{123}I) Injection] is a radiopharmaceutical product approved in Europe that was developed for assessing the integrity of dopaminergic nigrostriatal neurons. As an analogue of cocaine, the active substance [^{123}I]ioflupane binds to the pre-synaptic DaT protein found on dopaminergic nigrostriatal neurons in the brain; radioactive decay of the iodine-123 releases gamma radiation which allows visualization of the striata through SPECT imaging. Characteristic image patterns allow the facile determination of a patient's striatal status as normal or abnormal. Abnormal images indicate a SDD; i.e., loss of dopaminergic nigrostriatal neurons.

The primary objective of the current study was to determine the sensitivity and specificity of the visual assessment of DaTSCAN™ images in differentiating between PS/PD (which involves SDD) from non-PS conditions such as ET (which do not involve SDD).

The sensitivity of the visual assessment of DaTSCAN™ SPECT ranged between 94.9% and 97.5% for "consensus" (majority) BIE and on-site reads in the ITD population, respectively; specificity was between 93.5% and 98.4% for "consensus" (majority) BIE and on-site reads in the ITD population, respectively. Results in the PP population were similar. It should be noted that this was achieved in spite of the number of imaging and referring sites in 4 countries involved, and in spite of the heterogeneity of camera types and manufacturer. Sub-analyses on the basis of age, H&Y, and UPDRS score, and administered radioactivity revealed no significant differences in findings, thus verifying that disease pathology (i.e., the presence or absence of nigrostriatal dopaminergic degeneration) is the major discriminating factor. Agreement between the 5 BIE readers was excellent, with Cohen's κ values ranging from 0.83 to 0.92; the pooled coefficient for all 5 readers was 0.87. Agreement between the BIE readers and the on-site reads was similar, with Cohen's κ ranging from 0.88 to 0.94.

Since the completion of this study, the potential clinical utility of DaTSCAN™ in assisting with the diagnosis of patients with suspected PD has been recognized by the Royal College of Physicians in its National Institute for Health and Clinical Excellence (NICE) guidelines [Royal College of Physicians, 2006]:

> "The diagnosis of PD remains clinical. ^{123}I-FP-CIT SPECT may be of additional help in a small proportion of clinically uncertain cases. The diagnostic error rate on presentation may be as high as 10% in expert hands, which may lead to inappropriate therapy and distress following revision of the diagnosis."

13.2 Safety Discussion

Consistent with previous findings, the results of the present study indicate DaTSCAN™ to be a safe and well-tolerated radiopharmaceutical. Among the 224 subjects in the safety population,

36 subjects (16%) experienced a total of 69 AEs and only 2 AEs were severe (PD exacerbation (1 subject) and headache (1 subject)). Fifteen subjects (7%) experienced 32 AEs that were considered related to DaTSCAN™; the most common related AEs were headache (7 subjects) and vertigo, hunger, and formication (paresthesia) (3 subjects each). One SAE of PD exacerbation was reported and was not deemed to be related to DaTSCAN™. No safety concerns were noted in the results for clinical laboratory tests, vital signs, or ECG.

13.3 Overall Conclusions

Despite significant advancements in understanding the pathophysiology of PS/PD (SDD), there is no widely accepted biomarker. Practicing physicians and research investigators therefore continue to rely on clinical diagnosis, which has been shown to have high sensitivity at the expense of specificity, or vice versa.

In the present study, the assumption used in sample size estimation was that the sensitivity and specificity of DaTSCAN™ would each be 95%. Although no formal tests of significance were conducted, the point estimates for sensitivity and specificity from the on-site read (the primary endpoints) were 97.5% and 98.4%, respectively, which surpassed the assumptions made in sample size estimation. For the blinded reads, the sensitivity and specificity were 94.9% and 93.5%, respectively, nearly as high as the on-site reads.

The high sensitivity and specificity of both reads implies that DaTSCAN™ may help improve the diagnostic assessment of patients, which is currently based on clinical diagnosis and tends to have high sensitivity but low specificity. For example, Jennings [2004] reported that in evaluating patients with suspected PS for whom there was diagnostic uncertainty, referring neurologists collectively had a sensitivity of 92% and a specificity of 30%. The prevalence of PS in that study was 25/35, or 71%. Using these numbers, the PPV and NPV for detecting/excluding a SDD were calculated (using Bayes Theorem) for different pre-test probabilities of a SDD. The calculations were performed for both the clinical diagnosis and the blinded visual assessment of DaTSCAN™ images. The results (Table 21) show that DaTSCAN™ would perform better at detecting or excluding a SDD than clinical diagnosis at most pre-test probabilities of a SDD, and would be no worse at any pre-test probability.

However, DaTSCAN™ is not intended to be used in isolation as a diagnostic tool; rather, it is intended to be a supplement to clinical information. The combination of the information from DaTSCAN™ and clinical information can be viewed as the equivalent of sequential testing, first with the clinical assessment, and second with DaTSCAN™. This combination makes for an even more powerful diagnostic assessment, as the following example of a typical clinical evaluation illustrates.

Suppose a patient has a pre-test probability of a SDD of 70% and the clinical assessment is positive for a SDD-related disorder. The post-test probability of a SDD would then be equal to the PPV of the clinical diagnosis. In Table 21, a pre-test probability of 70% corresponds to a PPV of 75% for the clinical diagnosis. If the patient then is referred to DaTSCAN™ imaging, then the post-test probability of a SDD after clinical assessment (75%) can be viewed as the pre-test probability before DaTSCAN™ imaging. Finding the pre-test probability of 75% in

the table, it can be seen that if the DaTSCAN™ assessment is positive, then the post-DaTSCAN™ probability of a SDD would be 98% (the PPV for DaTSCAN™ at a pre-test probability of 75%), virtually ruling in a SDD. On the other hand, if the DaTSCAN™ imaging is negative for a SDD, then the post-test probability of a SDD would be equal to 100% minus the NPV of DaTSCAN™ at a 75% pre-test probability, which would give the probability of a SDD as 100% minus 86%, or 14%, which would cast serious doubt on the presence of a SDD and most likely lead the physician to consider another cause of the patient's symptoms.

Given the above, DaTSCAN™ would clearly be an extremely useful tool to physicians in the evaluation of patients with movement disorders.

Table 21 Positive and Negative Predictive Values for Clinical Diagnosis and DaTSCAN™ Visual Assessment

Pre-Test Probability of a SDD	PPV[a]		NPV	
	DaTSCAN™	Clinical Diagnosis	DaTSCAN™	Clinical Diagnosis
0%	0%	0%	100%	100%
5%	43%	6%	100%	99%
10%	62%	13%	99%	97%
15%	72%	19%	99%	96%
20%	78%	25%	99%	94%
25%	83%	30%	98%	92%
30%	86%	36%	98%	90%
35%	89%	41%	97%	87%
40%	91%	47%	96%	85%
45%	92%	52%	96%	82%
50%	94%	57%	95%	79%
55%	95%	62%	94%	75%
60%	96%	66%	92%	71%
65%	96%	71%	91%	67%
70%	97%	75%	89%	62%
75%	98%	80%	86%	56%
80%	98%	84%	82%	48%
85%	99%	88%	76%	40%
90%	99%	92%	67%	29%
95%	100%	96%	49%	16%
100%	100%	100%	0%	0%

PPV = Positive Predictive Value; NPV = Negative Predictive Value; SDD = Striatal Dopaminergic Deficit.
[a] Sensitivity and specificity assumed respectively to be 94.9% and 93.5% (DaTSCAN™) and 92% and 30% (Clinical Diagnosis).

The results indicate that the particular strength of functional presynaptic, dopaminergic imaging with DaTSCAN™, lies in its ability to reliably "rule in" and "rule out" SDD in patients with symptoms and signs of movement disorder. By adding DaTSCAN™ SPECT imaging to the diagnostic algorithm early on, inaccurate diagnosis and subsequent initiation of inappropriate therapy can be reduced.

To conclude, the results of the present study indicate DaTSCAN™ SPECT imaging to be a reproducible and useful tool with high sensitivity and specificity for detecting SDD in patients with symptoms and signs of movement disorder. This ability has been recognized as a clinically useful tool by the Royal College of Physicians in its National Institute for Health and Clinical Excellence (NICE) guidelines on PD.

14 TABLES AND FIGURES REFERRED TO BUT NOT INCLUDED IN THE TEXT

[14.1] Demographic Data Tables and Figures

[14.2] Efficacy Data Tables and Figures

[14.3] Safety Data Tables and Figures

[14.3.1] Displays of Adverse Events

[14.3.2] Listings of Deaths, Serious and Other Significant Adverse Events

14.3.3 Narratives of Deaths, Serious and Other Significant Adverse Events (refer to Section 12.2.2)

15 REFERENCE LIST

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16 APPENDICES

16.1 Study Information

[16.1.1] Protocol and Amendments
[16.1.2] Sample Case Report Form
[16.1.3] List of IECs and Representative Written Information for Subjects, and Sample Consent Forms
[16.1.4] List of Investigators and Other Study Personnel, and Curricula Vitae
[16.1.5] Signatures Pages
[16.1.6] Listing of Subjects Receiving Each Batch of Investigational Medicinal Product(s)
[16.1.7] Randomization Scheme and Codes
[16.1.8] Audit Certificates
[16.1.9] Documentation of Statistical Methods
[16.1.10] Documentation of Inter-Laboratory Standardization and Methods and Quality Assurance Procedures
16.1.11 Publications Based on the Study (None)
16.1.12 Copies of Important Publications Referenced in the Report (Refer to Section [15])

16.2 Subject Data Listings

Not presented.

16.3 Case Report Forms Submitted

[16.3.1] CRFs for Deaths, Other Serious Adverse Events, and Withdrawals for Adverse Events

16.3.2 Other CRFs Submitted

Not presented.

16.4 Individual Subject Data Listings

Not presented.

Department of Health

MEDICINES CONTROL AGENCY

Market Towers 1 Nine Elms Lane London SW8 5NQ

Telephone 0171-273-0327
Facsimile 0171-273-0443
Room 1418

Dr King
NYCOMED AMERSHAM PLC
Amersham Laboratories
White Lion Rd
Amersham
BUCKS HP7 9LL

Our Ref 00221/0134/A 63691
Your Ref PDT 03004

14 December 1998

Dear Dr King

THE MEDICINES (EXEMPTION FROM LICENCES)(CLINICAL TRIALS) ORDER 1995 (S.I. 1995/2808)
THE MEDICINES (EXEMPTION FROM LICENCES AND CERTIFICATES) (CLINICAL TRIALS) ORDER 1995 (S.I. 1995/2809)
PRODUCT: FP-CIT INJECTION
PROTOCOL: PDT 03004

I am writing to confirm that the Licensing Authority raises no objection to the change(s) in your submission of 30 November 1998, relating to the above-mentioned Protocol Code.

This trial may therefore proceed under the conditions previously agreed.

Yours sincerely

MR Jane Ann

MHRA
Safeguarding public health

Medicines and Healthcare products Regulatory Agency
Market Towers
1 Nine Elms Lane, London SW8 5NQ

Tel: 0207 084 2327
Fax: 0207 084 2443
Room No. 12-242

RECEIVED
14 JUN 2004

10 June 2004

Dr Claire Hill-Venning
Regulatory Advisor
Amersham PLC
The Grove Centre
White Lion Road
Amersham
Buckinghamshire
HP7 9LL

Dear Dr Hill-Venning

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 (S.I. No. 1031)
CLINICAL TRIALS EXEMPTIONS PRIOR TO 1 MAY 2004
RE: CTX 00221/0134/A

This letter is being sent to you because you requested that, from 1 May 2004, your Clinical Trials Exemption (CTX 00221/0134/A) be treated as an authorised clinical trial for protocol below.

The transitional provisions of paragraph 4 of Schedule 12 to the Regulations would appear to apply to your current exemption and in accordance with paragraph 4(2)(a) we are treating it as an authorised clinical trial for the purposes of the Regulations.

Please note that your CTA numbers are as follows:

Protocol PDT 304	CTA 00221/0134/001
Protocol PDT 301	CTA 00221/0134/002

Under the Regulations new duties are placed on the sponsors of clinical trials.

Briefly, a sponsor has a duty to:

- Identify who will be responsible for performing the various duties.
- Notify the relevant ethics committee and the MHRA and obtain their approval for any substantial amendments to the trial.
- Supply investigational medicinal products (IMPs) in accordance with the regulations.
- Make arrangements to conduct the trial in accordance with the principles of good clinical practice (GCP). The MHRA accepts the ICH GCP principles as the current standard.

I

Clinical Study Report
PDT03004

GE Healthcare

Title: AN OPEN, PHASE III CLINICAL STUDY TO ASSESS THE STRIATAL UPTAKE OF AN INTRAVENOUS SOLUTION CONTAINING THE DOPAMINE TRANSPORTER RADIO-LIGAND, DaTSCAN, IN PATIENTS WITH EARLY PARKINSONISM (US VERSION)

Authorisation:

Name	Capacity	Date
Horgan Kevin	Global Head Clinical	24-01-2009 07:07:41

US Version

GE Healthcare Ltd. and its Affiliates (hereinafter referred to as the "sponsor")

Clinical Project Leader
Paul Sherwin, MD
101 Carnegie Center
Princeton
NJ 08540
USA
Tel: +1 (609) 514 6820
Fax: +1 (609) 514 6855

Study Initiation Date: 18 Jan 1999
Study Completion Date: 28 Jun 2005

This study was conducted in compliance with Good Clinical Practices, according to the ICH Harmonised Tripartite Guideline.

Confidentiality Statement

1 DOCUMENT HISTORY

Study Title:	An open, phase 3 clinical study to assess the striatal uptake of an intravenous solution containing the dopamine transporter radio-ligand, DaTSCAN™, in patients with early Parkinsonism (US Version)				
Version Number	**Original Status**	**Date**	**Change Status**	**Date**	**Reason**
1.0	Effective	19/12/2008	Draft	22/01/2009	Changes in the adverse event (AE) SDTM and Analysis datasets resulted in an additional AE being flagged as causing a discontinuation in the study. Consequently, the following tables and listings changed: • Overall Summary of Adverse Events by Timing of Dose – Safety Population tables (Tables 14.3.1.1.1.a and 14.3.1.1.1.c) • 14.3.2.3 Listing of Discontinuations Due to Adverse Events – Safety Population The study report was updated to reflect this change.
2.0	Effective	Refer to title page			

2 SYNOPSIS

Name of Sponsor/Company: GE Healthcare Ltd. and its Affiliates **Name of Finished Product:** DaTSCAN™ **Name of Active Ingredient:** [^{123}]FP-CIT (Ioflupane)	**Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented:** **Volume:** **Reference:**	**(For National Authority Use only)**

Title of Study: An Open, Phase 3 Clinical Study to Assess the Striatal Uptake of an Intravenous Solution Containing the Dopamine Transporter Radio-Ligand, DaTSCAN™, in Patients with Early Parkinsonism (US Version)

Investigators and Study Centers: Ten centers in Europe participated in this study.

Investigators and Centers for Independent Evaluation of Images: The blinded image evaluation (BIE) of [^{123}I]FP-CIT (DaTSCAN™) Single Photon Emission Computed Tomography (SPECT) images was performed by 3 independent readers at the Image Review Centre (IRC) in Oslo. The independent image evaluation (IIE) video assessment (standard of truth [SOT]) was performed by 2 movement disorder specialists (MDS) at locations mutually agreed with the sponsor.

Publication (reference): Benamer HT, Oertel WH, Patterson J, Hadley DM, Pogarell O, Höffken H, Gerstner A, Grosset DG: Prospective Study of Presynaptic Dopaminergic Imaging in Patients with Mild Parkinsonism and Tremor Disorders: Part 1 Baseline and 3-Month Observations. *Mov Dis* 2003; 18:977-984.

Study Period: 18 January 1999 to 28 June 2005 | **Phase of Development:** 3

Objectives:

This study report is a US version prepared from the 2 original European clinical study reports (CSRs). The reasons for preparing a US version were:

(1) Integration of the 2 European CSRs for this study, 1 report for the main study phase and 1 for the follow-up phase.
(2) Conversion of the CRF data to CDISC SDTM format and the analysis data to '99 compliant format.
(3) Focus on key endpoints of clinical relevance.
(4) To present data in accordance with FDA guidance.

Primary objective: The original primary objective was to determine the predictive value of DaTSCAN™ SPECT to differentiate between subjects with early features of Parkinsonism (Parkinsonian syndrome [PS]), and other causes of tremor (mainly essential tremor [ET]), and healthy volunteers. The revised primary objectives are presented below.

Secondary objective:

The original secondary objectives were to assess safety parameters (hematology, biochemistry, urinalysis, vital signs and electrocardiogram [ECG]), and the adverse event (AE) profile in subjects, following a single intravenous (i.v.) injection of DaTSCAN™. The revised secondary objectives are presented below.

Study Design: This was a phase 3, multicenter, open, non-comparative, non-randomized, single-administration (at time of imaging) study in subjects with early PS. The study was designed to assess the safety and efficacy of DaTSCAN™ (111–185 Megabecquerel [MBq]) uptake in subjects with early signs of PS, other causes of tremor (mainly ET), and healthy volunteers at 3 time points (baseline [T = 0], 18 months [T = 18], and 36 months [T = 36]) over a 36-month period.

Selection of Subjects: Subjects with the clinical features of early PS or tremor (mainly ET) were eligible for this study. Healthy volunteers were selected from either a group of individuals known to the investigator or via advertisement at the study site.

Main Inclusion Criteria:

Subjects with Early Parkinsonism (PS):

(1) Subjects of either sex within the age range of 30 to 90 years.
(2) Subjects with cardinal features of Parkinsonism, i.e., bradykinesia and rigidity and/or tremor fulfilling

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Name of Active Ingredient: [^{123}]FP-CIT (Ioflupane)	**Volume:**	
	Reference:	

step 1 Brain Bank criteria or subjects with any single cardinal feature of Parkinsonism only if the diagnosis was not clear, i.e., possible ET or benign tremulous PD not fulfilling step 1 Brain Bank criteria.
(3) Unified Parkinson's Disease Rating Scale (UPDRS) part III scoring of 16 or less.

Healthy Volunteers:
(1) Healthy volunteers of either sex within the age range of 30 to 49 years.
(2) Healthy volunteers with a good age-appropriate health condition as established by clinical examination during screening.

Number of Subjects:
Planned: 180
Enrolled: 202
Received study drug: 179
Evaluable for safety (safety population): 179 (T = 0, after first dosing)
Evaluable for efficacy (per-protocol [PP] population): 102 (at T = 36, primary efficacy population

Treatment of Subjects:
Investigational Medicinal Product: DaTSCAN™, a single i.v. injection within the dose range of 111 to 185 MBq (3 to 5 mCi).
Control, Comparator: Not used.
Imaging: DaTSCAN™ SPECT images were acquired between 3 to 6 hours after DaTSCAN™ injection. The imaging lasted approximately 40 to 60 minutes.
Standard of Truth: Consensus expert clinical diagnosis established by 2 independent MDS by means of an IIE video assessment, as an indicator of nigrostriatal dopaminergic neuron loss. The expert clinical diagnosis was based on the assessment of a video taken at T = 36 months in combination with additional clinical information as described in detail in the IIE protocol for the video assessment.
Duration of Treatment: Single IMP administration at 3 time points: T = 0, T = 18, and T = 36.

Statistical Analyses:
Originally, there were 2 European clinical study reports (CSRs), one for the interim analysis (after the 18-month follow-up), and one final report which reported the integrated interim and final results after the 36-month follow-up. In support of a US New Drug Application, this CSR was prepared using data from both CSRs combined. The discussion in this CSR is focused on endpoints that are considered of greatest clinical and/or regulatory relevance. This resulted in a simpler presentation of the results that will be easier to review. The original data were converted to CDISC-compliant format.
The statistical analysis plan for the US CSR does not include all of the analyses specified in the study protocol. Results for the analyses not specified here can be found in the European PDT304 CSR. One analysis not specified in the original protocol is presented here, as listed under Secondary Endpoints below.
Tabulations of summary statistics, graphical presentations, and statistical analyses were performed using SAS® Software (Version 9.0). All continuous variables were summarized by the following descriptive statistics: number of subjects (N), number of subjects in a subgroup (n), mean, standard deviation (SD), median, minimum (Min), maximum (Max). Discrete variables were summarized by counts and percentages. Other parameters were tabulated as appropriate.
Primary Efficacy Variables:
In the reanalysis for the US CSR, sensitivity and specificity for the detection or exclusion of a SDD will be the focus of discussion. The clinical diagnosis established at 36 months was used as the SOT. Subject groups were defined as:
(1) Probable PD
(2) Possible PD
(3) Non-PD (e.g., subjects with ET)

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	Reference:	

(4) Other
Sensitivity and specificity of the visual image assessments for detecting or excluding a SDD were determined for the following comparisons:
(1) Probable PD (indicating the presence of a SDD) vs. non-PD (indicating the absence of a SDD);
(2) Possible or probable PD vs. non-PD; and
(3) Probable PD vs. Possible PD or non-PD.
These comparisons were done for the on-site clinical diagnosis (pre-DaTSCAN™) at T = 0. Sensitivity and specificity for detecting or excluding a SDD were determined for each BIE reader as well as for the on-site DaTSCAN™ read, and exact 95% confidence intervals (CI) were determined.
All of the above comparisons were done separately for the T = 36 SOT evaluations and for the PP and intent-to-diagnose (ITD) study populations at each of the read time points (T = 0, T = 18, and T = 36).
In addition the sensitivity and specificity (for detecting or excluding a SDD) of the visual image assessments and the on-site clinical diagnosis at baseline and at T = 18 were determined using the interim (18-month) SOT; the results are reported for each video reader separately (because no meetings were held to reach consensus in cases of disagreement between the 2 readers) and the mean sensitivity and specificity for the 3 BIE readers and the 2 video reviewers are also reported.

Secondary Efficacy Variables:
Inter-reader agreement is summarized for the ITD population. Inter-reader agreement with respect to the DaTSCAN™ SPECT visual assessment findings (abnormal/normal) were assessed using kappa (κ) statistics.

Safety Variables:
Only AEs were analyzed for the US CSR. A description of all other safety variables are presented in the European PDT304 CSR.
Adverse events were coded according to Medical Dictionary for Regulatory Activities (MedDRA) Version 11.0. The proportions of subjects with 1 or more AEs were summarized using counts and percentages.

Summary of Results:
The results of the sensitivity and specificity analyses are presented in this CSR. Results for accuracy, positive predictive value (PPV), and negative predictive value (NPV) are presented in the European PDT304 CSR.

Efficacy:
The sensitivity of DaTSCAN™ SPECT imaging for detecting or excluding a SDD in comparison to the SOT (independent consensus clinical diagnosis at 36 months) ranged from 77.5% to 78.6%, depending on the DaTSCAN™ SPECT image reader. The specificity was 96.8% for all 3 independent readers and 90.3% for the on-site SPECT reader. A good sensitivity was thus achieved along with an almost perfect specificity: the 3 independent SPECT readers classified only the image of 1 subject, deemed to be non-PD according to the truth standard, as abnormal (false positive). Because there were almost no false positive decisions nearly all positive (abnormal) SPECT-based decisions are true positive. This means that if a DaTSCAN™ SPECT image is abnormal, the clinician can be very confident that the subject has a SDD.
On-site clinicians at baseline (T = 0) showed a definite tendency to over-diagnose a SDD (as indicated by the clinical diagnosis of PD). The sensitivity was high (93.0%), whereas the specificity was low (51.6%), indicating a high false-positive rate.
The rates of inter-reader agreement among the 3 blinded readers was extremely high. These results indicate that if the reconstruction and processing of the image is done correctly, a subject can be assured that a DaTSCAN™ SPECT based classification will generally be identical regardless of the nuclear physician analyzing the image. This, together with the stability of the image findings over time, verifies the robustness of the visual assessment.
Comparison of the SPECT reads at T = 18 and T = 36 to the SPECT read at T = 0 revealed no large differences,

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	Reference:	

showing that DaTSCAN™ images were very consistent over time.
The kappa value for agreement between the 2 MDS video readers (used to determine the SOT) was 0.37 at T = 18 and 0.68 at T = 36, both lower than the rate of inter-reader agreement for DaTSCAN™ images.

Safety:

Among the 179 subjects in the safety population, 122 subjects (68%) experienced a total of 400 AEs. Of these, 32 subjects (18%) experienced 71 non-fatal SAEs. Four subjects (2.2%) experienced SAEs that resulted in death: 1 related to bronchial carcinoma, 1 the result of cardio-respiratory failure after hip fracture, 1 caused by septicemia and the fourth to respiratory failure secondary to multi-morbidity. None of the SAEs were deemed to be related to DaTSCAN™.

The majority of the AEs (376 AEs, 94%) were deemed by the investigator not to be related to DaTSCAN™. The most frequently reported AE was headache (15% of subjects).

Only 24 AEs (6.0%) were considered as having reasonable relationship to DaTSCAN™, most of which were mild in intensity (14, 3.5%). The most common AEs with reasonable relationship to DaTSCAN™ were: headache (5 subjects, 3%), followed by nausea (3 subjects, 2%), injection site hematoma, dizziness, and dysgeusia (2 subjects each, 1%).

All laboratory values for serum biochemistry, hematology, and urinalysis data showed general stability over time with no clinically significant mean changes from baseline or trends indicative of a safety concern.

Group mean values for vital signs showed stability over time when compared to baseline. No significant trends indicative of a safety concern were apparent.

No significant effects of DaTSCAN™ administration on ECG waveform were detected. None of the observed ECG waveform abnormalities were accompanied by changes in subject management. ECG intervals were not measured. In summary, no ECG abnormalities or trends indicative of a safety signal were detected.

Changes in physical examination after DaTSCAN™ administration were infrequent, minor and were not accompanied by changes in subject management or by AEs.

Conclusions:

Despite significant advancements in our understanding of the patho-physiological features of movement disorders such as PS, there is no widely accepted biomarker. Practicing neurologists and research investigators continue to rely on a diagnosis based on clinical examination, which has low specificity. The results of the present trial verify that DaTSCAN™ can detect the loss of nigrostriatal dopaminergic neurons in patients with symptoms and signs of a movement disorder (such as early PS) with high sensitivity and specificity. The clinician can thus reduce the rate of false positive decisions and the initiation of inappropriate therapy wit possible side effects. The high inter-reader agreement rates verify the robustness of DaTSCAN™ SPECT visual assessment, as does the stability of the findings over time.

Both the clinical and image findings in the present study were based on independent blinded reads rather than on-site assessment of the data. However, in the routine clinical setting neuro-imaging findings are used as an adjunct to the neurologist's overall clinical assessment. The nuclear physician as well is supplied with important aspects of the subject's history. The higher sensitivity and specificity obtained when DaTSCAN™ SPECT results were compared to the on-site clinical diagnosis after 36 months illustrate the impact of additional and "in person" clinical information on diagnostic accuracy.

Overall, the results of this 3-year follow-up verify DaTSCAN™ imaging to be a robust, reproducible and useful tool for objectively detecting loss of nigrostriatal dopaminergic neurons.

Among the 179 dosed subjects evaluated for safety, there was overall stability through the follow-up period for all parameters, including clinical laboratory, vital signs and ECG. No clinically important safety signals or trends over time were noted.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
[^{123}I]FP-CIT	[^{123}I]-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)-nortropane
AE	Adverse event
ARSAC	Administration of Radioactive Substance Advisory Committee
ATC	Anatomical Therapeutic Chemical (system of drug classification)
BIE	Blinded image evaluation
BMI	Body mass index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COD	Confidence of diagnosis
CRF	Case report form
CSR	Clinical study report
CT	Computed tomography
DaT	Dopamine transporter
DaTSCAN™	[^{123}I]FP-CIT
DLB	Dementia with Lewy bodies
DSM IVR	Diagnostic and Statistical Manual of Mental Disorders (4th Revision)
DVD	Digital video disc
ET	Essential tremor
ECG	Electrocardiogram
EMEA	European Medicines Evaluation Agency
FN	False negative
FP	False positive
GCP	Good Clinical Practice
H&Y	Hoehn and Yahr
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IIE	Independent image evaluation
IMP	Investigational medicinal product
IRC	Image review center
ITD	Intent-to-diagnose
i.v.	Intravenous
MDS	Movement disorder specialists
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MSA	Multiple system atrophy
NPV	Negative predictive value
PD	Parkinson's Disease
PP	Per-protocol

Abbreviation	Definition
PPV	Positive predictive value
PS	Parkinsonian syndromes
PSP	Progressive supranuclear palsy
PT	Preferred Term
SAE	Serious adverse event
SD	Standard deviation
SDD	Striatal dopaminergic deficit
SOC	System Organ Class
SOP	Standard Operating Procedure
SOT	Standard of truth
SPECT	Single Photon Emission Computed Tomography
T = 0	Time point of study procedures performed at baseline
T = 18	Time point of study procedures performed 18 months post-baseline
T = 36	Time point of study procedures performed 36 months post-baseline
TN	True negative
TP	True positive
UK	United Kingdom
UPDRS	Unified Parkinson's Disease Rating Scale
WHO-ART	World Health Organization Adverse Reactions Terminology
WHO-DD	World Health Organization Drug Dictionary

5 ETHICS

5.1 Independent Ethics Committee or Institutional Review Board

Before the study was initiated, the protocol was submitted to and approved by or received a favorable opinion from, an Independent Ethics Committee (IEC) according to national or local regulations. Any protocol amendments were also submitted for relevant approval. A list of all IECs consulted and the name of each committee's chair is appended in Section [16.1.3].

5.2 Ethical Conduct of the Study

This study was conducted in full accordance with the 1996 revision of the Declaration of Helsinki, the *Good Clinical Practice (GCP): Consolidated Guideline* approved by the International Conference on Harmonisation (ICH), and any applicable national and local laws and regulations.

The investigators were responsible for performing the study in accordance with the clinical study protocol and ICH E6-GCP, for collecting, recording, and reporting the data accurately and properly. Agreement of the investigator to conduct and administer this study in accordance with the clinical study protocol was documented in separate study agreements with the sponsor and other forms as required by national authorities in the country where the study center was located.

The principal investigator at each center was responsible for the conduct and administration of the study at that center, and for contacts with study center management, the IEC, and with local non-regulatory bodies.

5.3 Subject Information and Informed Consent

Written and oral information about the study in a language understandable to the subject was given to all subjects. The information provided an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force.

Written informed consent was obtained from each subject before any procedures or assessments were done and after the aims, methods, anticipated benefits, and potential hazards were explained. It was explained to the subjects that they were free to decline entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

The subject's willingness to participate in the study was documented in writing in a consent form that was signed by the subject with the date and time of signature indicated. The investigators kept the original consent forms and copies were given to the subjects.

Copies of the sample informed consent form and any other written information provided to the subjects are appended in Section [16.1.3].

5.4 Authority Approval

Written and dated approval was obtained from the following radiation safety boards or isotope committees regarding the use of DaTSCAN™ in the Germany and the UK:

Country	Radiation Safety Board/Isotope Committee
Germany	Bundesamt für Strahlenshutz (BfS)
UK	Administration of Radioactive Substances Advisory Committee (ARSAC), Department of Health

Clinical study clearance from the relevant regulatory/health authorities was obtained in all countries before the start of the study. For sites in the Germany and the UK, the sponsor and the investigators agreed not to recruit any subjects into the study before receiving a favorable opinion from the applicable radiation safety board or isotope committee.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The sponsor conducted, monitored, and performed statistical analyses and reporting of the study. Data management was performed on behalf of the sponsor by Statwood, Bevan House, 9-11 Bancroft Court, Hitchin Herts SG5 1LH, UK.

The study drug, DaTSCAN™, was manufactured by, and delivered from, Amersham Health B.V., Den Dolech 2, 5612 AZ, Eindhoven, The Netherlands, to the radiopharmacy or directly to the department of nuclear medicine at each study site referenced in Table 1.

Ten study centers were initiated; the 10 sites enrolled a total of 202 subjects. Table 1 provides a list of principal investigators and shows the number of subjects enrolled and the number administered DaTSCAN™ at each site.

Table 1 List of Investigators and Subject Enrolment

Center Number	Principal Investigator	Center Location	Number of Subjects Enrolled[a]/Administered DaTSCAN™ [b]
001	Dr. D. Grosset	Department of Neurology Southern General Hospital 1345 Govan Road Glasgow G51 4TF, Scotland	86/75
002	Professor W. Oertel	Medizinisches Zentrum für Nervenheilkunde/Klinik für Neurologie Klinikum der Phillips-Universität Marburg Rudolf-Bultmann – Strasse 8 35039 Marburg, Germany	34/34
003	Dr. H. BenAmer	New Cross Hospital EEG Department Wednesfield Road Wolverhampton WV10 0QP, UK	9/8
004	Dr. P. Kemp	Southampton General Hospital Department of Nuclear Medicine Tremona Road Southampton SO16 6YD, UK	9/8
005	Dr. D. Burn	Newcastle General Hospital Westgate Road Newcastle upon Tyne NE4 6BE, UK	29/29
006	Professor E. Tolosa	Hospital Clinic i Provincial Servicio de Neurologia c/Villarroel no. 170 08036 Barcelona, Spain	20/17

Table 1 List of Investigators and Subject Enrolment

Center Number	Principal Investigator	Center Location	Number of Subjects Enrolled[a]/Administered DaTSCAN™ [b]
007	Dr. J. Kulisevsky	Servicio de Neurologia Hospital de la Santa Creu i Sant Pau Paseo San Antonio Maria Claret, 167 08025 Barcelona, Spain	8/2
008	Dr. T. Vander Borght	Department of Nuclear Medicine University Hospital UCL Mont-Godinne 5530 Yvoir, Belgium	1/0
010	Professor L. Cunha	Servico de Neurologia Hospitais da Universidade de Coimbra Av. Bissaya Baretto P-3000-075 Coimbra, Portugal	6/6
011	Professor. W. Poewe	Leopold-Franzens-Universität Innsbruck Universitätsklinikum für Neurologie Anichstr. 35 A-6020 Innsbruck, Austria	0/0

[a] Assigned a subject study number
[b] Dosed with DaTSCAN™ at least once

A list of investigators and other important study personnel, including documentation of each investigator's qualifications, is appended in Section [16.1.4].

An independent blinded image evaluation (BIE) of the DaTSCAN™ single photon emission computed tomography (SPECT) images obtained in this study was performed according to the BIE Protocol (Section [16.1.1]). The BIE was conducted at the Image Review Center (IRC) in Oslo, Norway. The 3 independent blinded readers who participated in the read are listed in Table 2. Details of the conduct can be found in Section 9.1.1.

Table 2 Independent Blinded SPECT Read

Name	Address	Blinded Read Modality/Function
Prof. Dr. D. Costa	HPP Medicina Molecular, SA Avenida da Boavista, 119 4050-115 Porto, Portugal	DaTSCAN™ SPECT BIE reader
Dr. J. Booij	Department of Nuclear Medicine, F2N Academic Medical Center Meibergdreef 9 1105 AZ Amsterdam, The Netherlands	DaTSCAN™ SPECT BIE reader
Professor Dr. Klaus Tatsch	Abteilung für Nuklearmedizin Klinikum Großhadern Marchioninistr 15 81377 München, Germany	DaTSCAN™ SPECT BIE reader

The standard of truth (SOT) was the consensus expert clinical diagnosis as determined by 2 independent movement disorder specialists (MDS) on the basis of relevant clinical information and a video showing the Unified Parkinson's Disease Rating Scale (UPDRS)

part III assessments. An independent image evaluation (IIE) of the videos was performed according to the IIE protocol (Section [16.1.1]). The IIE was conducted at locations agreed between the sponsor and the 2 MDS who served as video readers. The 2 MDS are listed in Table 3. For details of the conduct, please refer to Section 9.1.2.

Table 3 Movement Disorder Specialists who Conducted Independent Image Evaluation of Video Assessments

Name	Address	Independent Read Modality/Function
Dr. G. Ulm	Paracelsius-Elena-Klinik Klinikstraße 16 34128 Kassel, Germany	IIE video assessment reader
Dr. K. Ray-Chaudhuri	Flat C 190 Bedford Hill London SW1 29HL UK	IIE video assessment reader

All laboratory samples were analyzed by MediLab Ltd., Mumberry House, New Barn Lane, Leigh, Lancashire, WN7 3UD, UK.

Electrocardiograms (ECGs) were not centrally analyzed but evaluated at the study centers by qualified physicians.

7 INTRODUCTION

Assessment of patients with symptoms and signs of movement disorders and dementia remains a formidable challenge, despite advances in knowledge of the pathophysiology of these conditions. One new approach is based on research showing that some of these disorders have in common the progressive, irreversible loss of a specific type of neuron, namely the dopaminergic nigrostriatal neuron. This type of neuron is found in the basal ganglia, which are nuclei (groups of neurons) in the brain that modulate both movement and cognition; consequently, conditions that affect the basal ganglia may result in movement disorders and/or dementia [Cote and Crutcher 1991; Martin 1996].

One especially key part of the basal ganglia is the substantia nigra pars compacta, a nucleus that contains pigmented dopaminergic neurons that project to, and synapse with, neurons in another nucleus called the striatum; these neurons are known collectively as the nigrostriatal pathway. They are referred to as dopaminergic because dopamine is the neurotransmitter that passes signals between neurons. Each of the two striata (left and right) is composed of two smaller regions called the caudate and putamen. The striata are depicted in Figure 1 (in green) as comma-shaped structures; the caudate nuclei form the "heads" of the "commas" and the putamen nuclei form most of the "tails".

Figure 1 3-Dimensional Diagram of Human Brain Showing the Striata (in Green) as Two Comma-Shaped Structures

Source: http://www.nimh.nih.gov/images/news-items/striatumcortex1.jpg

Dopaminergic nigrostriatal neurons bear a protein, the dopamine transporter (DaT) protein, which functions to stop inter-neuronal signaling by removing dopamine from the synapse. Dopamine re-uptake is achieved by high affinity binding to the DaT. In addition to binding dopamine tightly, the DaT protein also binds cocaine (a dopamine re-uptake inhibitor) and cocaine analogs with high affinity. Radiolabelled cocaine analogs have been developed for imaging of the dopaminergic nigrostriatal neurons where they synapse in the striata.

One such analog is DaTSCAN™ [Ioflupane (^{123}I) Injection], a radiopharmaceutical product that was developed for assessing the integrity of dopaminergic nigrostriatal neurons. The active substance in DaTSCAN™, [^{123}I]ioflupane, binds reversibly with high affinity to the DaT protein, thereby making it a specific marker for dopaminergic nigrostriatal neurons. The radioactive decay of the iodine-123 releases gamma radiation which allows visualization of the striata through SPECT imaging. Because DaTSCAN™ occupies less than 1% of DaT protein binding sites, there are no cocaine-like pharmacologic effects (about 60% occupancy is needed for cocaine-like effects).

Following intravenous (i.v.) injection (111 to 185 MBq, or 3 to 5 mCi) of DaTSCAN™, [^{123}I]ioflupane is distributed rapidly to the striata, reaching stable activity levels within approximately 3 hours. It provides a stable imaging window of approximately 3 to 6 hours. DaTSCAN™ images depict normal striata (Figure 2) as symmetric comma or crescent shaped areas of increased activity (increased brightness). Abnormal striata lack activity in some regions and thus appear as incomplete structures (Figure 3). In the most severe cases, striatal activity may be completely absent. These characteristic image patterns allow the facile determination of a patient's striatal dopaminergic status. In Parkinson's disease (PD) patients, autopsy studies have consistently revealed that approximately 60% of dopaminergic nigrostriatal neurons are lost before the onset of symptoms; because the loss is so extensive, it is readily apparent in DaTSCAN™ images of patients with symptoms and signs of movement disorders. Thus, quantification of the image data is not needed to differentiate normal and abnormal striatal images.

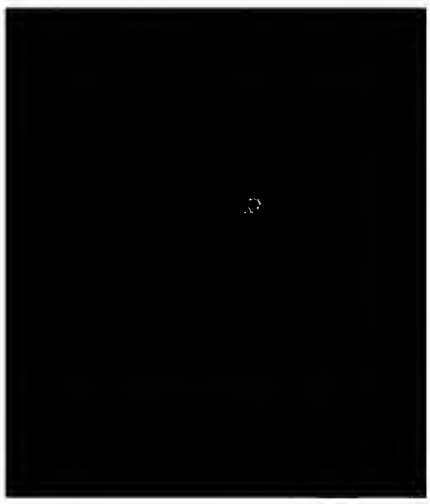


Figure 2 DaTSCAN™ ([^{123}I]Ioflupane) SPECT image in a healthy subject showing striata as bright "comma"-shaped regions

Figure 3 DaTSCAN™ (^{123}I]ioflupane) images showing areas of reduced striatal signal indicative of the loss of nigrostriatal neurons in a patient with early PD

Several autopsy studies have established that there is extensive loss of dopaminergic neurons in some degenerative movement disorders and dementia, such as **PD** [Victor 2001; Fahn 2003;

Bernheimer et al. 1973; Ma et al. 1997; Pakkenberg et al. 1991; Rinne et al. 1989; Beal et al. 1994], **multiple system atrophy** (MSA) [Wenning et al. 1997; Kume et al. 1993], **progressive supranuclear palsy** (PSP) [Hardman et al. 1997], and **dementia with Lewy bodies** (DLB) [Piggott et al. 1998], but little loss in others such as **Alzheimer's disease** (AD) [Torack and Morris 1992; Kemppainen et al. 2002], **Pick's disease** [Yokota et al. 2002], and **Huntington's disease** [Bernheimer et al. 1973].

The loss of dopaminergic nigrostriatal neurons is thus common to several neurodegenerative conditions (Parkinsonian syndromes [PS], PD, MSA, PSP, and DLB), but is not specific to any one. Accordingly, the abnormal DaTSCAN™ image patterns found in patients with conditions associated with a striatal dopaminergic deficit (a SDD) would be similar because the patterns are a function of uptake by the neurons, and this reduced uptake is mechanistically the same across these conditions. A DaTSCAN™ image simply provides visual evidence of the presence or loss of DaT function, indicating the presence or loss of dopaminergic nigrostriatal neurons.

Short of autopsy, there is no diagnostic test that can diagnose the specific condition associated with the neuron loss, so current diagnosis still rests on clinical examination. However, the accuracy of clinical diagnosis is dependent upon both the duration of illness and examiner expertise. Diagnosis is easier the longer the patient has had the condition (because new symptoms may develop and the symptoms profile may better fit the typical presentation of one of the diseases in the differential diagnosis). Sub-specialists in movement disorders or dementia tend to diagnose more accurately than general neurologists, who in turn diagnose more accurately than primary care physicians. Thus, clinical diagnosis can be in error in a significant percentage of cases [Hughes et al. 1992; Walker et al. 2007], or may be delayed. Improvement in neurodiagnosis is urgently needed, and DaTSCAN™ may help fill that need. Adding knowledge of the patient's striatal dopaminergic status (as indicated by DaTSCAN™ images) to the clinical information already used in neurodiagnosis may be useful in differentiating between conditions associated with a SDD and those which are not (but which may have similar clinical presentations); this differentiation may help facilitate an earlier accurate diagnosis in patients with movement disorders or dementia. Because an erroneous diagnosis may result in inappropriate therapy with possible complications [Hensman and Bain 2006; Hagenah et al. 1999], the benefits of an earlier accurate diagnosis are that the patient may receive appropriate therapy earlier, and the physician can avoid medications that are unnecessary or that may actually be detrimental (e.g., some neuroleptics have dangerous side effects in patients with DLB) [McKeith et al. 2005; Mosimann and McKeith 2003; Aarsland et al. 2005].

DaTSCAN™ was approved under a European Marketing Authorization granted in July 2000. Since that time it is estimated that approximately 168,000 patients have been administered with DaTSCAN™. In Europe, the information provided by DaTSCAN™ is used to help resolve clinically uncertain cases. A New Drug Application is being filed in the US, and the study results reported here will form part of the submission.

The primary objective of the present PDT304 study was to determine the predictive value of DaTSCAN™ SPECT to differentiate between subjects with early features of Parkinsonism (with a SDD), other causes of tremor without a SDD (mainly essential tremor [ET]), and

healthy volunteers (no SDD). The SOT used to determine if a subject had a SDD or not was the consensus expert clinical diagnosis established by 2 independent MDS, based on the assessment of a video recording of a neurological examination at T = 36 months in combination with additional clinical information as described in detail in the IIE protocol for the video assessment.

In the patients enrolled in this study, the main feature differentiating between PS and non-PS is the presence or absence of a SDD. Thus, in the clinical context of a patient presenting with symptoms and signs of a movement disorder, detection of a SDD may lead a physician to diagnose PS, and the absence of a SDD may lead a physician to diagnose (or look for) a non-PS condition such as ET. Like all other DaT imaging agents, DaTSCAN™ can only determine the presence or absence of a SDD, and cannot determine which disease is associated with the SDD. Thus, DaTSCAN™ (and all other DaT imaging agents) cannot diagnose a specific disease such as PD; that diagnosis must be made by the physician using all available clinical information along with the information provided by DaTSCAN™ imaging. However, the information provided by DaTSCAN™ regarding the presence or absence of a SDD would assist the physician in the differential diagnosis of patients with movement disorders.

Although the original results of the main and follow-up phases were reported in 2 separate European CSRs (1 for the main phase and 1 for the follow-up), this study has been identified as principal in support of the proposed indication for the US market. Therefore, a US version of the CSR has been prepared, primarily to update the tables and figures resulting from conversion of the data to a '99-compliant format. In addition, the original main study report and follow-up study report have been integrated into a single CSR for ease of review. Furthermore, the original European Statistical Analysis Plan has been reviewed by the sponsor and shortened by excluding those analyses considered to be redundant or non-contributory in support of the proposed indication for the US market. However, the full data set is available for review and analysis in this NDA submission.

8 STUDY OBJECTIVES

Primary

The original primary objective was to determine the predictive value of DaTSCAN™ SPECT to differentiate between subjects with early features of Parkinsonism, other causes of tremor (mainly ET), and healthy volunteers. The revised primary objectives are presented in Section 9.8.5.

Secondary

The original secondary objectives were to assess safety parameters (hematology, biochemistry, urinalysis, vital signs, and ECGs), and the adverse event (AE) profile in subjects, following a single i.v. injection of DaTSCAN™. The revised secondary objectives are presented in Section 9.8.5.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This was a phase 3, multicenter, open, non-comparative, non-randomized, single-administration (at time of imaging) study in subjects with early Parkinsonism.

The study was designed to assess the safety and efficacy of DaTSCAN™ (111–185 MBq) in subjects with early PS (a disorder known to involve a SDD), other causes of tremor (mainly ET; known not to involve a SDD) and healthy volunteers at 3 time points (T = 0, T = 18, T = 36) over a 36-month period.

The basic design was:

(1) Administration of DaTSCAN™.

(2) SPECT imaging of the brain.

(3) Visual assessment of images as either:

- normal (indicating no SDD) or
- abnormal (indicating a SDD).

(4) Determination of the SOT assessment at 36 months (as an indicator of striatal status) as either:

- non-PS/PD (indicating no SDD) or
- PS/PD (indicating a SDD).

(5) Comparison of each visual image assessment with the SOT assessment to allow classification as one of the following:

- True Positive (TP).
- True Negative (TN).
- False Positive (FP).
- False Negative (FN).

(6) Determination of sensitivity and specificity and other endpoints.

To avoid unnecessary exposure to radiation in healthy volunteers, data obtained from healthy volunteers in a previous DaTSCAN™ study (DP008-003) were used as the basis for how

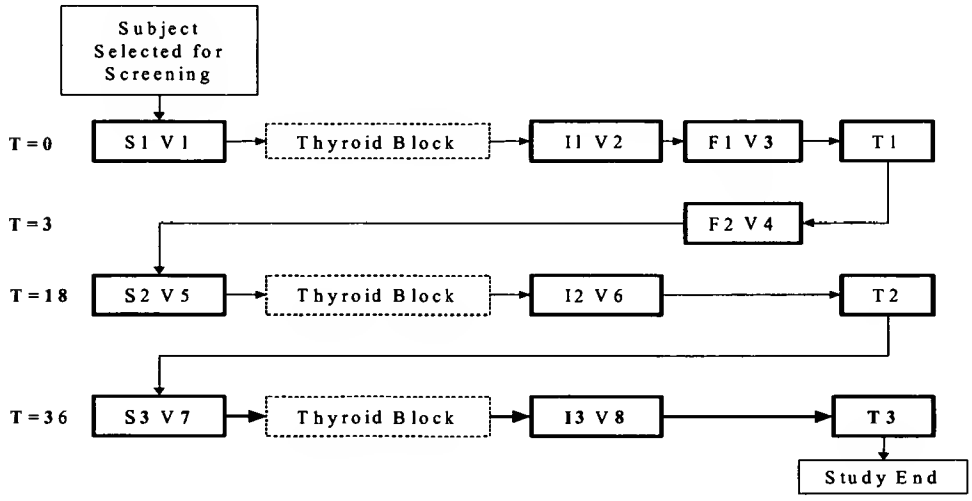
"normal" scans should appear. However, the protocol indicated that if patients aged 30 to 49 years were enrolled, it would be necessary to include 1 healthy volunteer with an age within the patient's decade. This was to allow investigation of any age-related changes in DaTSCAN™ uptake because no data existed for this age range at that time.

Throughout the study, information on diagnostic investigations not required by the clinical study protocol but related to Parkinsonism was collected: any computed tomography (CT), magnetic resonance imaging (MRI), and postsynaptic D2 dopamine receptor SPECT imaging as well as all challenge tests were recorded. Apomorphine and levodopa challenge tests for dopaminergic responsiveness represent a diagnostic tool in Parkinsonism as both substances produce comparable dopaminergic effects and can, in combination with motor tests, e.g., UPDRS, be used to measure dopaminergic motor response. The results of CT, MRI, and D2 imaging (if performed) were provided to the MDS making the SOT assessments.

The clinical diagnosis established at 36 months by the independent MDS is the SOT used to decide if a subject had a SDD (i.e., a loss of functional nigrostriatal dopaminergic neurons). However, similar assessments were also carried out at 18 months. These 2 examinations will be referred to as the "final SOT" (36-month assessment) and "interim SOT" (18-month assessment), respectively. Although the final SOT diagnosis made at 36 months is considered more robust, there was a relatively large number of dropouts before the 36-month assessment, so results based on the 18-month assessment (with greater numbers of subjects) were also determined.

Subjects were required to visit the study site on 8 occasions and to attend 3 telephone follow-ups. Figure 4 illustrates the sequence of these visits and telephone interviews.

Figure 4 Study Flow Chart



S = Screening; V = Visit; I = Imaging; T = Telephone Interview; F = Follow-up

- At the first screening visit (S1 V1), each subject was asked to provide written informed consent and the subject's eligibility for the study was assessed in accordance with the inclusion/exclusion criteria. Furthermore, subjects considered suitable for entry underwent a prespecified neurological examination, which was video-taped (following amendment 6).

- Eligible subjects attended the first imaging visit at T = 0 (I1 V2) within 4 weeks after screening. Prior to imaging they received a thyroid blocking preparation followed by a single i.v. dose of DaTSCAN™.

- SPECT imaging was performed 3 to 6 hours after injection.

- Post-imaging safety parameters were assessed by means of a T = 0 follow-up visit (F1 V3) and a telephone interview (T1).

- At the 3-month visit (F2 V4), the on-site diagnosis before and after viewing the T = 0 DaTSCAN™ image was established.

- The imaging visits at T = 18 (I2 V6) and T = 36 (I3 V8) followed the procedures for injection and imaging that were performed during the T= 0 visit (I1 V2). Imaging visits were preceded by a screening visit (S2 V5 and S3 V7), which included the video-taping of neurological assessments and establishing of an on-site clinical diagnosis, and were followed by a telephone interview (T2 and T3).

- Physical examination, clinical laboratory tests, vital signs, and ECGs were performed at various, prespecified time points.

- The occurrence of AEs was recorded throughout the 3-year year study period. For a detailed description of safety assessments, refer to Section 9.5.2.

The protocol and protocol amendments are appended in Section [16.1.1]. A sample case report form (CRF) is appended in Section [16.1.2].

Efficacy and safety measurements performed at the study centers and obtained during the course of the study are summarized in Table 4.

Table 4 Study Schedule

Time Point (Months after Study Entry)	**T = 0**				**T=3**	**T = 18**			**T = 36**		
Visits	**S1 V1**	**I1 V2**	**F1 V3**	**T1**	**F2 V4**	**S2 V5**	**I2 V6**	**T2**	**S3 V7**	**I3 V8**	**T3**
Procedures											
Informed consent	x										
Demographic information	x										
Inclusion/exclusion criteria	x										
Withdrawal criteria						x			x		
Medical and surgical history	x										
Neurological signs and symptoms	x				x	x			x		
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x
Physical examination	x	x	x								
Vital signs	x	x[1]	x				x[1]			x[1]	
ECG	x		x								
Laboratory	x	x	x								
Pregnancy test	x	x[2]	x				x[2]			x[2]	
Thyroid block – pre-injection[3]		x					x			x	
DaTSCAN™ injection		x					x			x	
SPECT imaging		x					x			x	
AEs	x[4]	x[4]	x	x	x	x[4]	x[4]	x	x[4]	x[4]	x
Hoehn &Yahr assessment	x				x	x			x		
UPDRS assessment	x				x	x			x		
Challenge test (optional)[5]	x				x	x			x		
Clinical impression/ diagnostic confidence	x[6]				x[6,7]	x[6]	x[7]		x[6]	x[7]	
Video-taping of neurological assessments[8]	x					x			x		

S=Screening, V=Visit, I=Imaging, T=Telephone Interview, F=Follow-up

[1] Pre- and post-injection

[2] Before DaTSCAN™ SPECT imaging

[3] Further thyroid blocking may have been given after the imaging visit if deemed relevant by the investigator

[4] Baseline symptoms and/or serious adverse events (SAEs) at T = 0, T = 18 and T = 36 screening (S2 V5, S3 V7)

[5] In symptomatic subjects

[6] Clinical impression / pre-DaTSCAN™ SPECT image diagnostic confidence

[7] Clinical impression / post-DaTSCAN™ SPECT image diagnostic confidence

[8] In symptomatic subjects only – if video assessment was not completed, subject was withdrawn from respective efficacy analysis. Baseline video added with protocol Amendment 6.

9.1.1 Blinded image evaluation of DaTSCAN™ SPECT images

The interpretation of the DaTSCAN™ SPECT images was performed by 3 independent blinded readers (3 nuclear physicians with extensive experience in neuro-imaging), according to a pre-written BIE protocol. The BIE was conducted at the IRC in Oslo, Norway (see also Section 6). A more detailed description of the BIE is provided in Section 9.5.1.

9.1.2 Independent image evaluation – video assessment

Two movement disorder specialists conducted independent evaluations of the video images of subjects undergoing neurological examinations. The objective of the independent image evaluation (IIE) was to contribute to establishing an independent clinical diagnosis to be used as the SOT in deciding whether or not a subject had a SDD (i.e., a loss of functioning nigrostriatal dopaminergic neurons). The SOT assessment was based on the IIE as well as other clinical information (but excluding DaTSCAN™ information and the on-site clinical diagnosis). An IIE was conducted at 18 months as well as at 36 months. The clinical assessment based on the 36-month data is considered the final SOT.

The 36-month evaluations were performed by 2 independent assessors (physicians experienced in the management of movement disorders). Initially each physician evaluated the subjects individually. A consensus session was then held to re-evaluate cases in which there was a mismatch between readers. This consensus expert clinical diagnosis served as the SOT. A more detailed description of the IIE is provided in Section 9.5.1.

The clinical assessment made based on the 18-month IIE and other data is considered the interim SOT. No consensus session was conducted at this time point to resolve inter-reviewer differences. Therefore, the 18-month results for sensitivity and specificity are presented below for each reviewer. The results based on the interim SOT are reported for comparison with the 36-month results, because a large percentage of subjects was lost to follow-up between the 18- and 36-month visits.

9.2 Discussion of Study Design

9.2.1 Justification for the efficacy analysis

The ability to reliably detect or exclude a SDD (i.e., loss of functional nigrostriatal dopaminergic neurons) would greatly assist clinicians in the differential diagnosis of patients with symptoms of movement disorders.

Sensitivity and specificity are well-accepted summary measures of the ability of a diagnostic agent to correctly classify a patient as having or not having a pathological finding of interest. In contrast to positive and negative predictive values (PPVs and NPVs), they do not depend on the prevalence of the abnormality being detected.

To determine whether or not DaTSCAN™ has correctly visualized a patient's striata as normal or abnormal, comparison with a SOT for striatal status is needed. It is well known from autopsy evidence that certain movement disorders (including PD, PSP, and MSA) are associated with loss of nigrostriatal dopaminergic neurons. Thus, a reliable diagnosis of PS (PD, PSP, or MSA) made by a MDS is a surrogate marker for the presence of a SDD, and thus can be used as a SOT. Conversely, an expert diagnosis of a non-PS condition is a surrogate for the *absence* of a SDD and can therefore be used as a SOT.

The reliability of a clinical diagnosis increases with the period of observation on which it is based. Thus, the clinical diagnosis based on the 36-month follow-up is more reliable than the one based on the 18-month follow-up, which is more reliable than the one made at study entry. This is because some movement disorders (such as PS) are progressive, and the clinical picture becomes clearer over time as symptoms and signs worsen.

In this study, patients were recruited at 9 centers in 5 countries. The use of 9 different MDS to render the SOT assessments would introduce variability. To reduce this variability, it was considered necessary to rely on fewer MDS, but it would have been impractical to have each MDS examine every patient. Therefore, it was decided to prepare videos of subjects being examined, and to provide the videos along with pertinent clinical information to 2 MDS who would then render the IIE and then the SOT assessments. In this way, variability could be reduced, for the SOT at 36 months. Videotaped examinations have been shown to have strong correlation with in-person examinations (91% for PD; 98% for non-PD; [Louis et al. 2002]).

An open study design was chosen as an approved comparator was not available.

The BIE was conducted to help avoid potential bias that could be introduced by knowing the subjects' signs, symptoms, and other information.

9.2.2 Justification for dose and volume

Pilot and formal clinical studies have demonstrated that visual assessment of DaTSCAN™ SPECT images permits detection of loss of dopaminergic nigrostriatal neurons and confirm that DaTSCAN™ can thereby discriminate PS (which involves a SDD) from ET (which does not involve a SDD) [Booij et al. 1997a; Booij et al. 1997b; Seibyl et al. 1998; Tissingh et al. 1998; Grosset 2000]. These results formed the basis of the marketing authorization approval for the use of DaTSCAN™ in Europe. The range of administered activity recommended in the European labeling is between 111 and 185 MBq. In prior clinical trials, this range of administered activity was well tolerated and was without pharmacologic effects or safety concerns, yet gave striatal images that were of diagnostic quality.

A lack of pharmacologic effects is expected based on the small mass dose of the active component of DaTSCAN™, [^{123}I]ioflupane, which is no more than 0.325 micrograms. This amount of material results in a DaT protein receptor occupancy of less than 1%, far below the approximately 60% receptor occupancy needed for pharmacologic effects from cocaine.

The recommended activity range provides sufficient flexibility to allow adjustment of activity to accommodate imaging systems of varying count sensitivity.

In this study, the 2.5 mL presentation of DaTSCAN™ (185 MBq [5 mCi] of DaTSCAN™ at reference time in 2.5 mL solution) was used.

9.2.3 Justification for prohibited and permitted medication

Agents with high affinity for DaT such as amphetamine, benztropine, buproprion, cocaine, mazindol, methylphenidate, phentermine and sertraline have the potential to interfere with DaT binding of [^{123}I]ioflupane; they were therefore prohibited in the study.

Even if a medication did interact with [^{123}I]ioflupane binding, such interactions would be homogeneous throughout the striata and thus would not result in asymmetries or changes in putamen/caudate ratios. Therefore, the accuracy of visual assessment of DaTSCAN™ images as normal or abnormal should not be affected.

9.2.4 Justification of the 18-month and 36-month follow-up

Originally the duration of a subject's participation in the study was to be 3 months. In March 2000, following approval of the marketing authorization application, the sponsor agreed to the following post-authorization commitments to the European Medicines Agency (EMEA) (see also Section 9.8, amendment 4):

> "The subjects had to be followed for 3 years from initial assessment. The 36-month follow-up had to include a clinical diagnosis by a physician experienced in the management of movement disorders and blinded to any previous clinical diagnosis. The 36-month follow-up also had to include an imaging session with DaTSCAN™. The initial and any subsequent DaTSCAN™ SPECT images were to be interpreted by a minimum of 3 independent reviewers who were blinded to the clinical diagnosis and had experience in the interpretation of DaTSCAN™ images. The sponsor was free to consider interim time points for an additional analysis."

The sponsor amended the protocol to extend the study and to address the post-marketing commitments. The sponsor also elected to include an interim analysis at 18 months.

9.2.5 Justification for the safety plan

This study's safety monitoring plan was justifiable and adequate from a safety standpoint in view of the following:

- The design of the safety plan permitted an appropriate and adequate evaluation of the safety response to DaTSCAN™ under baseline and post- DaTSCAN™ injection conditions in the same subject.
- The measures used to assess safety were well defined and reliable within the context of the SPECT imaging environment, and the proposed safety analyses were adequate to assess the effects of DaTSCAN™.
- Prior clinical studies with DaTSCAN™ have shown that it is well tolerated without pharmacologic effects or safety concerns.

- Consistent with the low mass dose (≤ 0.325 micrograms) the [^{123}I]ioflupane occupancy of the DaT protein binding sites is less than 1%, well below the approximately 60% occupancy needed for pharmacologic effects from cocaine.

- Post-marketing safety surveillance data have revealed no safety concerns, and no safety-related major revisions of labeling have been made.

9.3 Selection of Study Population

To meet the study objectives, it was necessary to find subjects who had a known SDD as well as those without. As discussed above, autopsy studies have shown that patients with certain subtypes of PS (including PD, MSA, and PSP) have a SDD. ET is a condition known not to be associated with a SDD. The study population thus consisted of subjects with the clinical features of early PD, tremor (mainly ET), and healthy volunteers. The subject's final status (SDD or not) was determined based on the consensus expert clinical diagnosis made at 36 months by MDS (experts in movement disorders) as a surrogate for autopsy evidence.

Symptomatic subjects were selected for screening from the movement disorder clinic databases or other general neurology clinics. Healthy volunteers were selected from either a group of individuals known to the investigator or via advertisement at the study site. It was planned that at least 30% of subjects within the total population should have a UPDRS score of 8 or less (see also Section 10.3.1).

A subject was enrolled into the study only if all inclusion criteria and none of the exclusion criteria were fulfilled. Written, dated, and witnessed informed consent was obtained from all subjects prior to study entry and prior to any protocol-specific procedures.

Selection criteria for subjects with symptoms of early Parkinsonism, tremor of unknown origin and healthy volunteers are listed separately for clarity of presentation. In the original European PDT304 CSR, inclusion and exclusion criteria are presented by criteria rather than by study population; here they are presented by study population.

9.3.1 Subjects with symptoms of early Parkinsonism

9.3.1.1 Inclusion criteria

(1) In the opinion of the investigator, the subject fully understood the implications of the study, and was able and willing to comply with the protocol requirements and visits to the study center at the required time points. Subjects were judged to be cooperative and gave their written informed consent to participate in the study.

(2) Subjects of either sex within the age range of 30 to 90 years.

(3) Subjects with cardinal features of Parkinsonism, i.e., bradykinesia and rigidity and/or tremor fulfilling step 1 Brain Bank criteria (group 1),

OR

Subjects with any single cardinal feature of Parkinsonism only if the diagnosis was not clear, i.e., possible ET or benign tremulous PD not fulfilling step 1 Brain Bank criteria (group 2).

(4) UPDRS part III scoring of 16 or less. An even spread of early Parkinsonism patients within this range was sought. At least 30% of subjects within the total study population had a UPDRS of 8 or below.

(5) Women who were post-menopausal (at least 2 years), surgically sterile or taking adequate contraceptive precautions (i.e., hormonal contraception or intrauterine device).

9.3.1.2 Exclusion criteria

(1) History of stroke or clinical evidence of cerebral vascular disease or presence of cerebral tumor or other structural lesion communicating hydrocephalus confirmed on CT or MRI, if appropriate.

(*Note*: CT or MRI were performed according to routine clinical practice).

(2) History of psychiatric illness other than depression.

(3) Positive Diagnostic and Statistical Manual of Mental Disorders (DSM IVR) (4th Revision) assessment for dementia.

(4) History of repeated head injury.

(5) History of definite encephalitis.

(6) Neuroleptic treatment at onset of symptoms or 1-methyl-4-phenyl-4-phenyl-1,2,3,6-tetrahydro-pyridine exposure.

(7) Features suggestive of MSA or PSP, such as

- Supranuclear gaze palsy.
- Cerebellar signs.
- Early severe autonomic involvement.
- Early severe dementia.
- Positive Babinski sign.

(8) Presence of known causes of tremor, such as

- Hyperthyroidism.
- Concurrent or recent exposure to tremorogenic drugs.
- Direct or indirect trauma to the nervous system within 3 months preceding the onset of tremor. This included head injury (direct or indirect), and peripheral injury, if the anatomical distribution of injury was the same as that of the tremor.
- Historical or clinical evidence of psychogenic origins of tremor. Clinical features that suggested non-physiological variations (>1 Hz) in tremor frequency, unusual and inconsistent behavioral characteristics, and spontaneous remissions. Psychiatric or social factors (multiple somatisations, secondary gain, litigation or compensation pending), supported the diagnosis of psychogenic tremor.

(9) History and response to drug therapy suggested idiopathic PD and the clinical history exceeded 5 years.

(10) Use of any concomitant medication that was known or suspected to interact with striatal uptake through direct competition with binding of DaTSCAN™ to the DaT.

(11) Presence of any medical condition that was known or suspected to interact with the pharmacokinetics of the test product, or iodine, e.g., renal and hepatic impairment.

(*Note*: For the purposes of this study 'renal impairment' was defined as serum creatinine levels 3-fold above the normal range, and 'hepatic impairment' as hepatic transaminase 3-fold above, or γ-Glutamyltransferase (γ-GT) 5-fold above the normal range).

(12) Known high sensitivity to iodine.

(13) Occupational exposure to radiation equal to, or above 15 mSv per year.

(14) History of abuse or current abuse of drugs and/or alcohol.

(15) Participation in a clinical study involving an unlicensed pharmaceutical product within the 3 months prior to screening, and/or an unlicensed/licensed radiopharmaceutical within 5 radioactive half-lives prior to screening.

(16) Previous enrolment in this study.

(17) Any laboratory value(s), with the exception of serum creatinine, hepatic transaminase, and γ-GT, exceeding the limits of normality by more than 10%, if deemed to be clinically relevant by the investigator.

(18) Women who were pregnant or lactating or planning a pregnancy during the course of this study or within 3 menstrual cycles of completing the study.

(19) Women of childbearing potential who were not taking adequate contraceptive measure (i.e., barrier methods such as condoms, diaphragm, and spermicides).

9.3.2 Healthy volunteers

9.3.2.1 Inclusion criteria

(1) In the opinion of the investigator, the volunteer fully understood the implications of the study, and was able and willing to comply with the protocol requirements and visits to the study center at the required time points. Volunteers were judged to be cooperative and gave their written informed consent to participate in the study.

(2) Healthy volunteers of either sex, aged between of 30 to 49 years.

(3) Healthy volunteers with a good age-appropriate health condition as established by clinical examination during screening.

(4) Women who were post-menopausal (at least 2 years), surgically sterile or taking adequate contraceptive precautions (i.e., hormonal contraception or intrauterine device).

9.3.2.2 Exclusion criteria

The exclusion criteria for healthy volunteers were the same as for the subjects with symptoms of early Parkinsonism.

9.3.3 Withdrawal of Subjects from the Study or from Assessment

Subjects were free to withdraw from the study at any time. The investigator could also withdraw a subject from the study if an illness or AE occurred, if the subject did not co-operate, or for any reason concerning the health or well-being of the subject.

If withdrawal occurred after administration of the DaTSCAN™ but before all evaluations were completed, efforts were made to complete the evaluations and report the observations as thoroughly as possible. A complete final evaluation was performed at the time of the subject's withdrawal, giving an explanation of the withdrawal. The reason, date and time of the withdrawal were recorded on the subject's CRF. If the reason for withdrawal was an AE or an abnormal laboratory test result, all efforts were made to monitor the outcome.

Subjects who withdrew from the study before the 18-month follow-up assessments were replaced up to the latest recruitment time point (June 2002). Those subjects who withdrew from the study after the T = 18 month follow-up assessments were not replaced.

9.4 Investigational Medicinal Product

9.4.1 Identity of investigational medicinal product

DaTSCAN™ ([^{123}I]ioflupane) is an isotonic solution for i.v. administration. The active substance, [^{123}I]ioflupane, binds with high affinity to the pre-synaptic DaT protein. The chemical name for [^{123}I]ioflupane is [^{123}I] N-ω-fluoropropyl-2β-carboxymethoxy-3β-[4-iodophenyl] nortropane).

Amersham Health B.V., Eindhoven, The Netherlands, supplied DaTSCAN™ at a concentration of 74 MBq (2 mCi)/mL (0.07 to 0.13 µg/mL of ioflupane) at calibration time in vials containing 2.5 mL. ^{123}I has a physical half-life of 13.2 hours. The product is referenced to 12:00 hours Central European Time 1 day after manufacture. For the 2.5-mL vial, expiry is 7 hours from the activity reference time stated on the label (31 hours from the end of manufacture). In this study, vials were labeled "for clinical studies only."

Sufficient quantities of fully characterized investigational medicinal product (IMP) were provided and manufactured, packaged, and labeled in accordance with Good Manufacturing Practice. Shipping of the study drug to the study sites and dispensing of it to each subject was recorded as part of the study documentation.

The investigator maintained accurate records of the receipt of the IMP from the sponsor, including the date of receipt and subject code numbers. Date of examination, batch/vial codes used, activity and volume per administration and start and end time of administration were recorded in each subject's CRF and the radiopharmaceuticals log. All DaTSCAN™ shipping and disposal was logged by each of the parties concerned. In addition, drug accountability was maintained at the study site using a drug accountability log signed and dated by the investigator or delegate.

For information regarding the batches/vials of DaTSCAN™ that were used in this study, refer to Section [16.1.6].

DaTSCAN™ has been authorized for marketing in the EU since 2000.

9.4.2 Storage

DaTSCAN™ was stored at room temperature (not above 25°C). Appropriate radiation precautions were observed during storage of the agent.

9.4.3 Preparation

Appropriate radiation precautions were to be observed during preparation of the agent.

9.4.4 Investigational medicinal product administration (route, dose, and dosage schedule)

DaTSCAN™ was injected with the subject supine. After the access into an arm vein had been established, each subject received a single i.v. injection of DaTSCAN™ with a total activity amounting to 111 to 185 MBq (3 to 5 mCi), but not exceeding 185 MBq. DaTSCAN™ was administered via slow (not less than 15 to 20 seconds) i.v. injection and was followed by a saline flush of approximately 5 mL. The exact amount of activity was measured before injection and was tailored to the particular imaging system involved. Appropriate radiation precautions were observed during use of the agent.

9.4.5 Comparator product

No comparator was used in this study.

9.4.6 Method of assigning subjects to treatment groups

Each subject was assigned to receive DaTSCAN™.

9.4.7 Rationale for dose selection in the study

Refer to Section 9.2.2 for the rationale for the recommended dose range (111 to 185 MBq). The actual activity for each subject was tailored to the specific imaging system used at each site, depending for example on the imaging system's count sensitivity.

9.4.8 Selection and timing of dose for each subject

Each subject received up to 3 single i.v. injections of DaTSCAN™ (at T = 0, T = 18, and T = 36) 3 to 6 hours before SPECT imaging, based on the results of an earlier phase 2 clinical study (CY96.FP.II) that showed this to be a suitable window for SPECT imaging.

9.4.9 Blinding

This study was an open-label study in which all subjects were to receive DaTSCAN™. Neither the investigators nor the subjects were blinded to the dose of DaTSCAN™ given. BIE readers were blinded to the subject's clinical information.

9.4.10 Prior and concurrent therapy or medication

9.4.10.1 Recording of prior and concurrent medications

Details of any prior, concurrent therapy, medication, changes in medication or procedural medication, given to or taken by a subject within 4 weeks before and up to the end of the

observation period, were entered in the CRF. The generic or trade name and indication of concurrent or prior medication were also recorded. All therapy and medication were coded according to the WHO-Drug Dictionary (DD), Anatomical Therapeutic Chemical (ATC) Index 2004.

9.4.10.2 Procedural medications

Prior to the administration of DaTSCAN™ each subject received a thyroid blocking preparation, in accordance with each study site's thyroid blocking protocol.

9.4.10.3 Prohibited medications

The investigator had to avoid the concomitant administration of any medication with known or suspected high affinity for DaT that could possibly interact with DaTSCAN™. In line with the SmPC, the list of prohibited concomitant medication stated in the protocol included:

- cocaine (a tropane)
- amphetamine, mazindol and methylphenidate (sympathomimetics)
- benztropine (an anti-cholinergic)
- buproprion (an atypical anti-depressant used for treating nicotine addiction) and sertraline (a SSRI anti-depressant) (see also Section 9.2.3).

The minimum washout period for all generally prohibited concomitant medications was 4 weeks before imaging. If a subject was taking prohibited medication that could not be withdrawn, or if during the pre-imaging and imaging phase the use of any prohibited medication became necessary for medical reasons, the subject had to be excluded from participation in the study. If one of the prohibited medications was withdrawn from a subject to satisfy inclusion/exclusion criteria, the investigator first sought agreement of the subject and then implemented an appropriate drug withdrawal regimen.

9.4.10.4 Non-prohibited medications

Medications that were not prohibited int this trial were:

- amantadine, trihexyphenidyl levodopa, budipine and selegiline (anti-parkinsonian medications)
- metoprolol, and propranolol (beta-blockers)
- primidone (an anti-epileptic)

In pre-clinical studies, pergolide showed no interference with DaTSCAN™ imaging (see also Section 9.2.3).

Dopamine agonists and antagonists acting on the postsynaptic dopamine receptors were not expected to interfere with DaTSCAN™ imaging and were therefore allowed to be continued if desired.

As medication may have influenced the clinical presentation of the subject during neurological assessments videotaped for the SOT, the subject had to be in the off phase, i.e., anti Parkinson medication had to be withdrawn for an appropriate length of time prior to study procedures.

9.4.11 Treatment compliance

The subjects received DaTSCAN™ under direct supervision of study personnel. Each injection volume and total radioactivity injected was independently checked and recorded in the CRF. The vial label, containing subject number and vial number, were attached to the subject's CRF.

9.5 Efficacy and Safety Variables and Measurements

Efficacy and safety measurements performed at the study sites and obtained during the course of the study are summarized in the study schedule of events (Table 4).

9.5.1 Efficacy measurements

DaTSCAN™ SPECT image acquisition

SPECT imaging was performed during the T = 0, T = 18, and T = 36 imaging visits. Prior to imaging, each subject underwent thyroid blocking, safety assessments, and DaTSCAN™ administration.

SPECT images were acquired for 40 to 60 minutes, beginning 3 to 6 hours after DaTSCAN™ injection, using either a multi-headed gamma camera or a multi-detector single slice system. The gamma camera system had to be capable of SPECT acquisition, reconstruction, and producing transverse slices with a clear visualization of the striatum (caudate nucleus and putamen). The reconstruction algorithm was recorded on the appropriate CRF page. The images were stored electronically and also included as color hard copies in the subjects' CRFs.

DaTSCAN™ SPECT image evaluations

DaTSCAN™ SPECT images were evaluated both on-site and by 3 independent BIE readers, using the classification scheme shown in Table 5. "Normal" images showed no evidence of a SDD; "abnormal" images showed a SDD.

Table 5 DaTSCAN™ SPECT Visual Image Assessment Classifications

DaTSCAN™ Image Classification	Criteria
Normal	Normal images were characterized by uptake of the tracer in both right and left putamen and caudate nuclei. The image was largely symmetrical with approximately equal levels of uptake on both left and right sides. Activity was contained close to the center of the image forming 2 crescent shaped areas of uptake.
Abnormal, Type 1	Uptake was asymmetric with almost normal or reduced putamen activity in 1 hemisphere and a more marked change on the other side. The reduction in uptake was likely to be found on the side opposite to the patient's first affected side, and was characterized by a significantly lower or absent uptake in the putamen. As a result uptake was limited to a roughly circular area.
Abnormal, Type 2	Uptake was significantly reduced in the putamen on both the right and left sides. Activity was confined to the caudate nuclei and forms 2 roughly symmetrical, circular areas.
Abnormal, Type 3	Uptake was virtually absent from both putamen and caudate nuclei on each side of the brain resulting in a significant reduction in contrast and the visualization of background activity throughout the rest of the image.
Other	Option provided if an image could not be assigned to any of the categories above or was deemed non-evaluable (this option was introduced only after amendment 4 and is not provided in the CRF for the on-site image evaluation at T = 0).

For efficacy analyses, the 3 abnormal image types were combined, to allow a binary division of images into 'Normal' and 'Abnormal' categories. Subjects with an image assessment of 'Other' had to be either classified as 'Normal' or 'Abnormal' or had to be excluded from the analysis. The decisions were made (without knowledge of the clinical outcome) at the second data review meeting held directly after data base lock.

On-site SPECT evaluation

A nuclear medicine physician blinded to the subjects' medical history at each study center (on site SPECT reader) reconstructed all of the SPECT images to the highest resolution possible using the available software. Details of the reconstruction algorithm were recorded in the CRFs as stated previously. Attenuation correction of the image data was performed where possible. The results of the on-site image assessment were recorded on the CRF.

Blinded image evaluation – visual assessment

Study sites provided the DaTSCAN™ SPECT scans as electronic raw image data sets on CD-ROMs or via File Transfer Protocol to the IRC. The data sets were quality checked and then randomized according to a plan produced by a sponsor's statistician (other than the assigned study statistician). The randomization codes were entered in the BIE CRFs. The BIEs were conducted in several sessions depending upon the availability of the images and the readers.

The interpretation of the DaTSCAN™ SPECT images was performed by 3 independent blinded readers. The DaTSCAN™ SPECT images were presented to the readers on validated IRC workstations. The readers were blinded to subject identification (ID), initials, ID of the institution, the names of investigators and study personnel, and all other clinical information except for the subject's age. With increasing age, the specific nigrostriatal DaTSCAN™

uptake decreases and the non-specific uptake increases. Thus knowledge of the subject's age was provided to the blinded readers during the evaluation of the SPECT images. The BIE readers performed the visual assessment of the image data independent from each other. The readers entered the results of the visual assessment (as per the criteria presented in Table 5 above) in the SPECT read CRF.

Standard of truth

The expert clinical diagnosis established at 36 months by the independent MDS was the SOT used to decide if a subject had a SDD, i.e., a loss of functional nigrostriatal dopaminergic neurons. However, similar assessments were also carried out at 18 months. These 2 examinations will be referred to as the final SOT (36-month assessment) and interim SOT (18-month assessment), respectively. Although the final SOT diagnosis made at 36 months is considered more robust, there was a relatively large percentage of dropouts before the 36-month assessment, so results based on the 18-month assessment (with greater numbers of subjects) was also determined.

The SOT diagnosis was made by the MDS based on videotaped neurological examinations as well as other clinical information (but excluding DaTSCAN™ information and the on-site clinical diagnosis).

Videos of Neurological Assessments

Neurological assessments (UPDRS part III) of the subjects performed during the T = 18 and the T = 36 screening visits were video-taped. For subjects included after amendment 6 (see Section 9.8.1.6) those assessments were also video-taped at T = 0. As medication may have influenced the clinical presentation of the subject during these assessments, the subject had to be in the off phase, i.e., anti Parkinson medication had to be withdrawn for an appropriate length of time prior to study procedures. Healthy volunteers did not undergo neurological assessments.

Independent Image Evaluation – Video Assessment

Study sites provided the original videos of the neurological assessments performed during the screening visits to the IRC. To allow long term storage of the data, the original videos were digitalized onto digital video discs (DVDs). Each track on the DVD corresponded to 1 video. The data were blinded and copied onto another DVD according to a randomization plan that was produced by a sponsor's statistician (other than the assigned study statistician) and that listed the subject ID, the visit number and the randomization number for each video. These blinded data were viewed by the readers; the original videos were sent back to the sites. The DVDs were stored at the IRC.

The evaluation of the videos was performed by 2 independent readers, who were blinded to the DaTSCAN™ image results of all subjects and to the subjects' on-site clinical diagnoses. For each subject, the following information was provided to the reader as printout of validated data from the study clinical database:

- The subject's age and sex.

- The first onset of symptoms.
- The dates of first diagnosis before inclusion of the subject into the study presentation.
- A description of symptoms (e.g., tremor, general slowing down, change in gait, etc.) and observation of the subject's progression over the period from T = 0 until the acquisition of the T = 36 video.
- Whether the symptoms were predominantly unilateral or bilateral.
- Whether the symptoms began on the right or left side.
- Whether tremor, if present, was improved by alcohol consumption.
- The subject's family history, in particular with regards to tremor.
- The date(s) and result(s) of CT, MRI, or perfusion SPECT, if performed.
- The on-site result for "rigidity" in the UPDRS part III motor examination at the time when the video was taken.
- The Hoehn and Yahr (H&Y) disease stage at all available time points.
- Medication administered up to the time point when the video was taken.

Readers were also provided all available prior video assessments.

Based on the evaluation of the T = 36 video and the information listed above, readers established a clinical diagnosis, which served as the SOT used to determine whether or not a subject had loss of dopaminergic nigrostriatal neurons. The readers entered the following information in the IIE CRF (video read CRF):

- Determination of the subjects' scores on different motor examinations according to the UPDRS part III.
- Clinical diagnosis (probable PD, possible PD, ET, 'Other').
- Level of confidence of diagnosis (COD).

The readers evaluated the videos independently of one another. In case of disagreement between the independent readers for a T = 36 video diagnosis, they re-evaluated the subject to come to a consensus diagnosis. The consensus diagnosis was entered into a separate CRF and served as the SOT to determine whether or not a subject had loss of dopaminergic nigrostriatal neurons. At T = 18 no consensus diagnosis was established.

To allow a comparison of the SOT assessment with the of the visual assessment of DaTSCAN™ images (to classify each image assessment as true or false positive or negative), a binary division of the SOT assessment (probable PD, possible PD, ET, 'Other') into PD (indicating a SDD) and non-PD (indicating no SDD) had to be made; probable PD and possible

PD were considered to be PD; ET was considered to be non-PD. 'Other' assessments were classified as non-PD with the following exceptions: subjects diagnosed with MSA, PSP, and PD of benign tremulous type were categorized as PD since these conditions also involve striatal dopaminergic degeneration. Healthy volunteers were classified as non-PD.

On-site clinical diagnosis

The on-site investigators (i.e., neurologists) established a clinical diagnosis at several time points:

- A "pre-scan assessment" (made prior to the next scheduled DaTSCAN™ imaging session) at T = 0, T=3, T = 18, and T = 36 months
- A "post-scan assessment" (made after viewing the latest DaTSCAN™ SPECT image of the subject) at T=3, T = 18, and T = 36 months

The investigators recorded the subjects' scores on the various motor examinations (UPDRS part III), their clinical diagnosis (probable PD, possible PD, ET, 'Other') and the level of confidence (in percent) in the CRF.

9.5.2 Safety Measurements

The investigators and the study safety officer reviewed the safety data throughout the course of the study.

The following safety data were collected and evaluated:

- Physical examination (general condition, respiratory tract, urogenital system, cardiovascular, gastrointestinal, nervous system, musculoskeletal, skin, hematological system and lymph nodes, endocrine system).
- ECGs (12-lead).
- Vital signs (systolic/diastolic blood pressure [BP], heart rate).
- Laboratory variables (hematology, biochemistry, urinalysis, and microscopy/culture where indicated).
- AEs (baseline signs and symptoms were recorded before DaTSCAN™ administration; AEs were monitored after dosing throughout the study period).

The timing of physical examinations, ECGs, vital signs, and laboratory assessments up to the third telephone follow-up (T3) was scheduled according to Table 6 below.

Table 6 Timing of Safety Assessments

	Vital Signs		12-Lead ECG	Lab Samples	Physical Exam
	BP	Heart Rate			
T = 0 Screening Visit (S1 V1):					
48 hours – 4 weeks pre-injection	*	*	*	*	*
T = 0 Imaging Visit (I1 V2):					
1-2 hours pre-injection	*	*		*	*
Injection					
4-7 hours post-injection	*	*			
T = 0 Follow-up Visit (F1 V3):					
24 –72 hours post-injection	*	*	*	*	*
T = 18 Imaging Visit (I2 V6):					
1-2 hours pre-injection	*	*			
Injection					
4-7 hours post-injection	*	*			
T = 36 Imaging Visit (I3 V8):					
1-2 hours pre-injection	*	*			
Injection					
4-7 hours post-injection	*	*			

9.5.2.1 Adverse Events

An AE was defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

The subjects were closely observed and questioned for any kind of AE during the study procedures and throughout the study period with non-leading questioning (e.g., 'Do you feel any different since your last assessment?'). The subjects were instructed to immediately report any symptoms and signs to the study staff (i.e., between formal observations). AEs were recorded until the last telephone follow up (T3).

Serious Adverse Events

A serious adverse event (SAE) was defined as an AE which was fatal, life-threatening, disabling or incapacitating, or which required or prolonged hospitalization, or was associated with congenital abnormality. In addition, any experience which the investigator regarded as serious or which suggested any significant hazard, contraindication, side effect or precaution that might have been associated with the use of the IMP had to be reported as an SAE.

Definition of life-threatening:

An AE was life-threatening if the subject was at immediate risk of death from the experience as it occurred, i.e., it did not include a reaction that might have caused death if it had occurred in a more serious form.

Definition of disabling/incapacitating:

An AE was disabling or incapacitating if it resulted in a substantial and/or permanent disruption of the subject's ability to carry out normal (baseline) life functions.

Adverse Event and Serious Adverse Event Reporting

All AEs reported by the subject or observed by the investigator and/or delegate during the course of the study or in response to the question "Do you feel any different since your last assessment?" were recorded. Baseline signs and symptoms were recorded before the administration of IMP. All AEs were recorded during the administration of the IMP and at least up to 7 days post-imaging for all subjects. At the 18-month and 36-month follow-up visit any SAEs were recorded.

An AE included any noxious, pathological, or unintended change in anatomical, physiological, or metabolic functions as indicated by clinical signs, symptoms, and/or abnormal laboratory findings occurring at any time during the study period whether or not considered to be related to the IMP. This included an exacerbation of pre-existing conditions or events, inter-current illnesses and IMP interactions. Anticipated day-to-day fluctuations of pre-existing conditions, including the disease under study that did not represent a clinically significant exacerbation or worsening were not considered as AEs.

All AEs reported by the subject or observed by the study center personnel were reported in the CRF. The following information regarding each AE was obtained: date and time of onset and end date and time, outcome, event course (intermittent/constant), intensity (defined below) whether it was serious (previously defined), relationship to IMP, any corrective therapy, and whether an AE caused withdrawal from the study (recorded on "study completion page").

An AE ongoing at a previous assessment had to be followed to resolution and the outcome had to be recorded in the subject's CRF. If a previously reported experience changed in frequency and/or severity during the study period, details had to be recorded in the subject's CRF.

The severity of all AEs was graded as mild, moderate, or severe using the definitions described below.

Mild:	The event was easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities or sleep.
Moderate:	The event was sufficiently discomforting and interfered with normal everyday activities or sleep.
Severe:	The event prevented normal everyday activities or sleep.

In addition to the investigator's own description of the AEs, each AE was encoded according to the Medical Dictionary for Regulatory Activities (MedDRA, Version 11.0) and the WHO Adverse Reactions Terminology (ART) dictionary of medical codes.

Any SAEs occurring during the study period, whether or not considered to be related to DaTSCAN™, were to be reported within 24 hours for death and life threatening and within 5 calendar days for all other SAEs to the sponsor by telephone. The investigator was advised regarding the nature of further information or documentation required, but in all cases a full written report of the event had to be provided. The investigators were advised not to wait to

receive additional information to fully document the event before notifying the sponsor of an SAE.

A summary of SAEs that were determined to be reportable by the sponsor were distributed to all investigators and forwarded by the investigators to their IECs and local health authorities, according to local regulations.

Assessment of causality

The causality of AEs was assessed as:

Not related:	The event was definitely not related to the IMP.
Unlikely:	There was a good reason to assume that the event is likely to be caused by something other than the IMP.
Suspected (reasonable possibility):	A causal relationship was possible, and could not be excluded.
Probable:	Good reasons and sufficient documentation to assume a causal relationship.

The degree of certainty with which an AE was attributed to the IMP (or alternative causes, e.g., natural history of the underlying disease, concomitant therapy) was determined by how well the experience could be understood in terms of the known pharmacology of the IMP, and documented reactions of a similar nature related to the IMP or other radionucleotides.

9.5.2.2 Clinical laboratory variables

During the course of the study, 3 blood and urine samples were taken. The first set of samples was collected at the screening visit at T = 0 (S1 V1) to assess the subject's eligibility, the second prior to injection of DaTSCAN™ at the T = 0 imaging visit (I1 V2), and the third was collected 24-72 hours post-injection at the T = 0 follow-up visit (F1 V3). The laboratory tests measured are listed in Table 7.

Table 7 Laboratory Variables Measured

Serum Biochemistry	Hematology	Urinalysis
Sodium	Hemoglobin	Dipstick:
Potassium	Hematocrit	Specific Gravity
Blood Urea Nitrogen (BUN)	Red blood cell (RBC) count	Leukocytes
Creatinine	White blood cell (WBC) count	pH
Albumin	Platelet count	Albumin
Total Bilirubin	Differential white cell count	Glucose
Aspartate Aminotransferase (ASAT/SGOT)	Prothrombin Time*	Ketones
		Urobilinogen
Alanine Aminotransferase (ALAT/SGPT)		Bilirubin
		Hemoglobin
Alkaline Phosphatase		Microscopy:
γ-Glutamyltransferase (γ-GT)		WBC
Lactate Dehydrogenase (LDH)		RBC
Creatinine Phosphokinase (CPK), MB and MM fraction		Crystals
		Casts
		Epithelial Cells
		Bacteria*

* Measured in addition to the parameters prescribed in the clinical study protocol

Laboratory reports were sent by fax to the investigational sites. In addition, 3-part NCR (no carbon required) copies were sent out by mail. The original was signed by the investigator. The original and 1 copy were provided to the sponsor, 1 copy was kept at the site. The investigator had to comment on those values which were marked as clinically significant and documented them as baseline signs, symptoms or concomitant circumstances (S1 V1 and I1 V2 pre-injection) and as AEs, respectively (all subsequent visits), if there was a clinically significant worsening. Interpretation of clinical notable laboratory test results were conducted with respect to the clinical situation of the subject and in accordance with the guidelines provided in the clinical study protocol.

Once AE notification was decided upon, the investigator was required to follow the procedure described for AE notification in the protocol, and document the clinically notable laboratory results in the subject's CRF. Any clinically notable laboratory finding was followed throughout the duration of the subject's participation in the study until the abnormal value normalized or returned to baseline.

9.5.2.3 Vital signs

Vital-sign measurements were performed 8 times and included measurement of heart rate and systolic and diastolic BP. BP and heart rate were obtained at the T = 0 screening visit, at the T = 0 imaging visit pre- and post-injection, at the T = 0 follow-up, and at the T = 18 and T = 36 imaging visits pre- and post injection.

For vital-sign measurement the subject was supine or recumbent and had been resting for at least 5 minutes. The subject had to be in the same position each time vital signs were measured. Measurement of BP was made on the arm contralateral to the site of IMP injection.

Any vital sign that was judged by the investigator as a clinically significant change (worsening) compared to pre-injection was considered an AE. Once AE notification was decided upon, investigators were required to follow the procedure described for AE notification, and document the clinically notable abnormality in the subject's CRF. Any clinically notable vital sign finding was followed throughout the duration of the subject's participation in the study until the outcome was known.

9.5.2.4 Electrocardiograms

A 12-lead ECG was recorded and evaluated twice for each subject: at the T = 0 screening visit (S1 V1) and the T = 0 follow-up visit (F1 V3) 24-72 hours post-injection. The investigator recorded and commented any abnormal findings in the CRF. Each 12-lead ECG tracing at each time-point was identified with the subject's initials, subject number, and date of recording and was signed, dated, and retained in the investigator's study record for each subject. ECG intervals (i.e., PR, QRS, QT, and RR) were recorded on each subject's CRF.

(a) Investigational site responsibilities

ECG readers (independent qualified physicians) interpreted standard 12-lead ECGs in accordance with the clinical study protocol. Interpretation of clinically notable interval data and abnormal waveforms was conducted with respect to the clinical situation of the subject. Any clinically significant abnormalities were recorded in the CRF by the investigator. Any changes post-injection that were considered clinically relevant were recorded as an AE.

Once AE notification was decided upon, investigators were required to follow the procedure described for AE notification, and document abnormal findings in the subject's CRF. Any clinically notable interval data or abnormal waveform findings were followed throughout the duration of the subject's participation in the study until the outcome was known.

(b) ECG core laboratory responsibilities

This is not applicable, as ECGs were not centrally analyzed but evaluated at the study centers by physicians independent of the study.

9.5.2.5 Physical examinations

A physical examination was performed at 3 time points: the T = 0 screening visit (S1 V1), the T = 0 imaging visit (I1 V2) 1-2 hours pre-injection, and the T = 0 follow–up visit (F1 V3).

Physical examination included an assessment for the presence or absence of abnormalities in the following: general condition, respiratory tract, urogenital system, cardiovascular, gastrointestinal, nervous system, musculoskeletal, skin, hematological system and lymph nodes, and endocrine system.

Any physical examination finding that was classified by the investigator as a clinically significant change (worsening) compared to baseline was considered an AE. The investigators were required to follow the procedure described for AE notification; the finding was to be documented in the subject's CRF and followed until the outcome was known.

9.5.2.6 Injection site monitoring

Injection site monitoring was performed within the scope of AE recording. Any abnormal finding that was new or represented a worsening from baseline was recorded as an AE. Investigators were required to follow the procedure described for AE notification and document the abnormality in the subject's CRF.

9.5.3 Appropriateness of measurements

All assessments and measurements were appropriate and regarded as standard medical practice.

9.6 Clinical Data Management

The handling of data, including data quality control, was performed on behalf of the sponsor by Statwood, Bevan House, 9-11 Bancroft Court, Hitchin, Herts SG5 1LH, UK.

Data management was carried out according to Statwood's standard operating procedures (SOPs). Programming was performed by the sponsor and complied with the sponsor's SOPs. Both data management and programming procedures complied with the regulatory guidelines (e.g., ICH-GCP). All data management processing procedures were described in a data management plan.

All electronic checks and/or derivations on the clinical data were documented in the electronic check document as part of the data management study file. The checks were tested and the document was approved by the sponsor before they were used to raise queries.

Completed CRFs were reviewed before data entry by the monitor for completeness (i.e., source data verification), consistency, and legibility according to the monitoring plan before the CRFs were sent to Statwood.

The data from the CRFs were entered into Statwood's clinical database system; a second entry verification was performed. Laboratory data were transferred electronically from the central laboratory to Statwood. At Statwood, laboratory data were checked prior to loading to ensure consistency to the CRF demographic data and planned visits. Results were checked electronically against ranges provided by the lab.

During the data validation process, electronic checking procedures were run to create queries on incomplete, inaccurate and inconsistent data. In addition, derivation procedures were run to perform pre-defined calculations on data.

All AE and symptom terms recorded in the CRF were auto-encoded according to the medical dictionaries and MedDRA, medication was auto-encoded according to the WHO-DD, and all medical and surgical history terms were coded using the International Classification of Diseases (ICD) -9 dictionary. All coding entries were reviewed, corrected, and approved by the sponsor.

Queries for clarification of data recorded in the CRF were answered, dated, and signed by the investigator. Changes were implemented in Statwood's database accordingly and the validation and derivation procedures were repeated until no resolvable errors remained.

SAE reconciliation was performed between Statwood's clinical database and the sponsor's Pharmacovigilance database.

After all data quality control steps were completed, the database was locked. The data were extracted from the database into SAS datasets (Version 8.2) and transferred to the sponsor for reporting and statistical evaluation. A final database audit was performed on 10% of the subjects, which were selected by random (approved error rate of ≤0.05%) and on 100% of the primary efficacy data (approved error rate of 0%).

Data management for the US analysis was carried out by i3Statprobe, a CRO based in the US. i3Statprobe's programming procedures complied with the regulatory guidelines (e.g., ICH-GCP). i3Statprobe received the raw datasets containing all information captured in the study CRF from the sponsor. A statistical programmer reviewed the CRF and determined how data variables linked to each section in the CRF. Once the programmer was comfortable with the location of the variables in the CRF, the programmer created specifications for reassigning variable names based on CDISC SDTM-compliant naming conventions. The programmer then created a CDISC SDTM-compliant dataset. The specifications were then validated by an independent programmer, who also created a CDISC SDTM-compliant dataset using the specifications and then compared that dataset with the raw dataset to ensure that the mapping was correct.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

A full statistical report is appended in Section [16.1.9] of this report.

9.7.1 Statistical plans

Tabulations of summary statistics, graphical presentations, and statistical analyses were performed using SAS® Software (Version 8.2). The last pre-administration observation was used as the baseline value for calculating post-administration values from baseline. All data obtained in the CRF and entered into the database were provided in separate data listings showing individual subject values. The planning and reporting of statistical analyses were carried out as described in the sponsor's SOPs governing clinical studies.

All summary tables and data listings were separated by clusters when appropriate. All continuous variables were summarized by the following descriptive statistics: number of subjects (N), number of subjects in a subgroup (n), mean, standard deviation (SD), median, minimum (Min), maximum (Max). Discrete variables were summarized by counts and percentages. Other parameters were tabulated as appropriate.

All statistical tests were carried out at the 5% level of significance, unless otherwise specified.

9.7.1.1 Study population variables

(a) Disposition of subjects

The number of subjects enrolled per center and overall as well as the number of subjects who completed each visit of the study were provided together with the information on accessing to safety and efficacy population. Completion status was tabulated per time point and overall, whereas reasons for discontinuation were tabulated separately.

The sponsor made any decisions regarding whether a subject or an individual value belonging to a subject were to be excluded from the evaluations when a protocol violation was considered to imperil the scientific aspects and interpretation of the study results. Protocol violations and subject management decisions (i.e., inclusion/exclusion of the subject from safety/efficacy population) are listed in Section 10.2.

(b) Demographic data

Demographic data (gender, race, age, height, weight, and body mass index [BMI]) were summarized using descriptive statistics. Gender and race were also summarized by counts and percentages. The age of a subject was calculated in years by date of birth minus date of inclusion date.

(c) Risk factors and medical history

Information on the subject's relevant medical and surgical history was provided. Counts and percentages of all parameters were provided together with the estimated, categorized duration (≤5 years, >5 years) and the condition (active, not active). The description of the abnormality/disease and surgical procedures was listed in the appendix together with the time of presence.

(d) Previous and concurrent medication

Any prior and concurrent therapy or medication, including indication, given to a subject from 4 weeks prior to the first dose of DaTSCAN™ and up to the end of the observation period, (during and after the examination) was tabulated by counts and percentages using WHO coding and grouped by primary and secondary classes if applicable.

(e) Investigational medicinal product and dose

With respect to DaTSCAN™ administration, the following parameters were presented using descriptive statistics: volume aspirated from vial for injection, radioactivity present immediately prior to injection, radioactivity present immediately after injection, and radioactivity injected. Tabulation of a zero check performed was made using counts and percentages.

9.7.1.2 Determination of the safety and efficacy population

(a) Determination of the safety population

All dosed subjects were included in the safety population; this comprised also subjects who had to be excluded from the efficacy population. The safety population consisted of more subjects than the efficacy population. Data of subjects who withdrew from the study before dosing were not used for safety evaluation but listed only. Withdrawal from the study prior to follow-up examinations or non-completed examinations were not criteria for exclusion from the safety population.

All subject listings were done for the safety population. Subjects in the safety but not in the efficacy population were listed together with the reasons for excluding them from efficacy population.

(b) Determination of the efficacy population

A subject was part of the primary efficacy population, if both the T = 0 DaTSCAN™ SPECT imaging assessment was performed and the consensus expert clinical diagnosis (final SOT) based on the T = 36 video assessment was established by 2 independent MDS. An exception was the 3 healthy volunteers: although no T = 36 video assessment was performed they were included in the efficacy population and were considered to be non-PD subjects with respect to subsequent analysis.

All SPECT images, whether or not evaluable, were sent to the IRC for independent evaluation. The 3 independent SPECT readers were provided with the SPECT images of all dosed subjects. Images, which the readers determined as non-evaluable due to DaTSCAN™ unrelated reasons were to be excluded from the efficacy analyses for the respective reader. In case of non-evaluability due to DaTSCAN™ related reasons the image was used for the efficacy analysis and classified as mismatch (FN or FP) when compared to the SOT.

The decision of whether to exclude a subject from the analysis and the classification of reasons for non-evaluability of SPECT images was performed by the study team during a data review meeting on 26 October 2005. The decisions made were described and documented in detail for each subject. The documentation (i.e., meeting minutes) is attached as an appendix to the statistical report.

For all endpoints and analyses comparing 2 time points with one another the number of subjects evaluable was defined as the number of subjects with evaluable data for both time points.

9.7.1.3 Efficacy variables

(a) Primary efficacy endpoints

(i) Sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) for a) the on-site SPECT read and b) the independent SPECT BIE readers at T = 0 compared to the clinical diagnosis established by 2 independent MDS in consensus, based on the assessment of a video taken at T = 36.

The primary endpoint for this study was to compare the specific striatal uptake of DaTSCAN™ at T = 0 with the final SOT, i.e., the consensus expert clinical diagnosis established by 2 independent MDS at T = 36, based on a video assessment in combination with relevant clinical information. The consensus expert clinical diagnosis was used to determine if a subject had a SDD (loss of dopaminergic nigrostriatal neurons).

One institutional SPECT read (conducted on-site at each study center) and 3 independent blinded SPECT reads were performed. The results of each were compared separately to the final SOT. From these 4 comparisons, sensitivity, specificity, accuracy, PPV (the proportion of subjects with an abnormal scan at T = 0 who were confirmed as having Parkinsonism (indicating the presence of a SDD) by the clinical diagnosis at T = 36), and NPV (the proportion of patients with a normal scan at T = 0 who were confirmed as not having Parkinsonism (indicating the absence of a SDD) by the clinical diagnosis at T = 36), were computed.

Each on-site SPECT reader was blinded to the subject's medical history and assessed whether the DaTSCAN™ SPECT image was normal or abnormal type 1, 2, or 3 (see Section 9.5.1). As a dichotomous division into normal and abnormal was required for subsequent statistical analyses, the 3 abnormal categories were grouped as abnormal.

Table 8 defines the classification of image assessments as TP, TN, FP, or FN.

Table 8 Classification of DaTSCAN™ Image Assessments

Standard of Truth (Clinical Diagnosis)	Evaluation of DaTSCAN™ SPECT Images		Row Total
	Abnormal (SDD present)	Normal (SDD absent)	
Abnormal (PS; SDD present)	True Positive (TP)	False Negative (FN)	TP + FN
Normal (non-PS; SDD absent)	False Positive (FP)	True Negative (TN)	FP + TN
Column Total	TP + FP	FN + TN	N

Calculations of PPV, NPV, sensitivity, specificity, and accuracy were:

$$\text{PPV} = \frac{TP}{TP+FP}$$

$$\text{NPV} = \frac{TN}{TN+FN}$$

$$\text{Sensitivity} = \frac{TP}{TP+FN}$$

$$\text{Specificity} = \frac{TN}{TN+FP}$$

$$\text{Accuracy} = \frac{TP+TN}{TP+FP+TN+FN}$$

In case an image could not be evaluated, a reason had to be specified by the reader. Only images assessed as non-evaluable due to reasons unrelated to DaTSCAN™ were excluded from efficacy analysis for the respective reader. In case of non-evaluability due to DaTSCAN™ related reasons the image was included in the efficacy analysis and classified as mismatch when compared to the SOT.

The asymptotic confidence intervals of the parameters were constructed by using the normal approximation to the binomial distribution.

$$CI_{95\%(p)} = p \pm SE(p) * u_{1-\alpha/2}$$

$$\text{With } SE(p) = \sqrt{\frac{p*(1-p)}{n}}$$

$$u_{1-\alpha/2} = 1-\alpha/2 - \textit{Quantile of the standard normal distribution}$$

(b) Secondary efficacy endpoints

(i) Secondary Endpoint A: Sensitivity, specificity, accuracy, PPV, and NPV for (a) the on-site SPECT read and (b) the independent SPECT BIE readers at T = 0 compared to the clinical diagnosis given by an on-site neurologist at T=3 (blinded to the results of the SPECT read).

Before the study was extended to the 3-year period, comparison of the on-site clinical diagnosis at T = 3 months as SOT with the on-site SPECT findings at T = 0 was planned as the main endpoint. These endpoints were determined as for the primary endpoint.

(ii) Secondary endpoint B: Sensitivity, specificity, accuracy, PPV, and NPV for a) the on-site SPECT read and b) the independent SPECT BIE readers at T = 0 compared to the clinical diagnosis established by 2 independent MDS at T = 18 and T = 36.

At T = 36 these diagnoses were obtained before the 2 MDS convened to reach a consensus diagnosis. At T = 18 no consensus read was performed. Table 9 gives an overview of all comparisons used for the calculation of sensitivity, specificity, accuracy, PPV, and NPV: calculations of the parameters and their confidence intervals (CIs) were performed in the same manner as for the primary endpoint.

Table 9 Comparisons for Endpoint B

Comparison	SPECT Reader	Time Point of SPECT Imaging	Independent Video Reader	Time Point of Video
1	Institutional read	T = 0	Video Reader 1	T = 18
2	SPECT Reader A	T = 0		
3	SPECT Reader B	T = 0		
4	SPECT Reader C	T = 0		
5	Institutional read	T = 0	Video Reader 2	
6	SPECT Reader A	T = 0		
7	SPECT Reader B	T = 0		
8	SPECT Reader C	T = 0		
9	Institutional read	T = 0	Video Reader 1	T = 36
10	SPECT Reader A	T = 0		
11	SPECT Reader B	T = 0		
12	SPECT Reader C	T = 0		
13	Institutional read	T = 0	Video Reader 2	
14	SPECT Reader A	T = 0		
15	SPECT Reader B	T = 0		
16	SPECT Reader C	T = 0		

(iii) Secondary endpoint C: Sensitivity, specificity, accuracy, PPV, and NPV for the on-site clinical diagnosis at T = 0 compared to the clinical diagnosis established by 2 independent MDS at T = 18 and T = 36.

This endpoint assessed the efficacy of the pre- DaTSCAN™ on-site clinical diagnosis established during the T = 0 on-site screening visit. It was analyzed in the same manner as the primary endpoint.

Sensitivity, specificity, accuracy, PPV and NPV were calculated using the final (T = 36) SOT. In addition the institutional clinical diagnosis at T = 0 was compared to each diagnosis established by the 2 independent MDS individually at T = 18 (consensus results are not available for the T = 18 time point).

The following comparisons were conducted:

Table 10 Comparisons for Endpoint C

Comparison	Read	Time Point of SPECT Imaging	Independent Video Reader	Time Point of Video
1	Institutional clinical diagnosis	T = 0	Video Reader 1	T = 18
2	Institutional clinical diagnosis	T = 0	Video Reader 2	T = 18
3	Institutional clinical diagnosis	T = 0	Consensus diagnosis	T = 36

(iv) Secondary endpoint D: Exploratory analyses of the groups of probable PD, possible PD, and non-PD as determined by the IIE video assessment at T = 36.

Sensitivity, specificity, accuracy, NPV, and PPV for the 3 independent SPECT BIE readers at T = 0 were calculated using the final (T = 36) SOT (clinical diagnosis established by 2 independent MDS at 36 months, in the same manner as for the primary endpoint). However, subjects diagnosed as "possible Parkinsonism" by the SOT were excluded from this analysis.

(v) Secondary endpoint E: Confidence levels of the clinical diagnosis of idiopathic PD.

The neurologists at each centre were asked to record the level of COD of their clinical diagnosis of idiopathic PD at various time points: at T = 0 screening (i.e., before first DaTSCAN™ imaging visit), and at T=3, T = 18, and T = 36 (before and after viewing the DaTSCAN™ SPECT image). Tables were provided containing summary statistics: the confidence was presented by diagnosis. Tables with summary statistics and listings of individual subject's results were prepared to compare the pre-scan with the post-scan confidence to reveal whether information from the DaTSCAN™ images had an effect on the investigator's level of confidence.

(vi) Secondary endpoint F: Sensitivity, specificity, accuracy, NPV, and PPV for the independent SPECT readers at T = 0 compared to the on-site clinical diagnosis at T = 18 and T = 36.

This endpoint was analyzed in addition to the endpoints planned in the clinical study protocol. Calculations were conducted in the same manner as that for the primary endpoint and secondary endpoint B, however, the DaTSCAN™ SPECT image results were not compared to the SOT, but rather to the on-site clinical diagnosis established during the T = 18 and T = 36 screening visits.

(vii) Secondary endpoint G: Analysis of the stability of DaTSCAN™ SPECT findings (institutional visual read and independent SPECT read) over time: sensitivity, specificity, accuracy, PPV, and NPV for both the institutional SPECT and the independent SPECT BIE readers at T = 18 and T = 36 compared to the consensus diagnosis established by 2 independent MDS at T = 36.

This endpoint was added to compare the DaTSCAN™ SPECT BIE findings of the primary endpoint (T = 0) with the results obtained at later time points (T = 18 and T = 36). The parameters were calculated in the same manner as for the primary endpoint.

(viii) Secondary endpoint H: Inter-reader agreement between DaTSCAN™ SPECT readers; inter-reader agreement between independent video readers.

Inter-reader agreement was summarized for the intent-to-diagnose (ITD) population. Agreement between each pair of DaTSCAN™ image readers with respect to the visual assessment findings (abnormal/normal) was assessed using kappa (κ) statistics. Cohen's κ coefficient of agreement between the readers was estimated with 95% CIs. Since its calculation uses an approximation (based on the normal distribution), although the maximum value for the κ coefficient is 1, it is possible for the upper limit of these CIs to exceed 1. In these cases, κ values >1 are to be interpreted as 1 (i.e., perfect agreement). κ is ≤0 when the observed agreement is less than or equal to chance and it equals 1 when there is perfect agreement. The stronger the agreement the higher is the κ value.

κ coefficients were calculated for agreement of the on-site SPECT readers and the independent SPECT BIE readers at T = 0, T = 18, and T = 36 regarding normal versus abnormal findings. In addition, agreement of the 2 independent MDS regarding a subject diagnosis of PD versus non-PD was determined for T = 18 and T = 36.

- Agreement for the 2 independent MDS at T = 36 regarding PD versus non-PD diagnosis.

Details for the calculation methods can be found in the statistical analysis report.

9.7.1.4 Safety variables

(a) Symptoms

Baseline signs and symptoms were coded according to MedDRA. The proportions of subjects with 1 or more symptoms were summarized using counts and percentages.

(b) Adverse events

AEs were coded according to MedDRA. For each time point the proportion of subjects with 1 or more AEs (or SAEs) was summarized for each center and overall, using counts and percentages.

(c) Clinical laboratory variables

The safety endpoints for laboratory data were:

- Descriptive values and changes from baseline.
- The occurrence of 1 or more changes from baseline greater than 40% and 80% of the span of the normal limits (not applicable for qualitative variables).
- Values out of range and clinically significant results.

Laboratory parameters were summarized by standard tables for continuous and quantitative variables. Absolute changes from baseline for all laboratory parameters were summarized in the same way. 95% CIs for the differences between baseline and the post-time point were calculated and added to the table. Scatterplots and shift tables of all post-administration versus baseline values were generated, and examined for trends and relatively large individual changes from baseline.

(d) Vital signs

The safety endpoints for vital signs parameters were:

- The occurrence of 1 or more changes from pre-injection to post-injection, greater than the following pre-specified magnitudes: 20 mm-Hg for systolic BP, 10 mm-Hg for diastolic BP, 10 beats per minute (bpm) for pulse rate (PR).
- The occurrence of post-injection values outside the normal limits and the occurrence of post-injection clinically notable values. All vital signs parameters were summarized by standard tables for continuous and quantitative variables.

Absolute changes from baseline for all vital signs parameters were summarized in the same way. 95% CIs for the differences between baseline and the post-time point were calculated and added to the table. Scatterplots and shift tables of all post-injection values versus pre-injection values were generated, and examined for trends and relatively large individual changes from baseline. Shift tables (above, below and within reference ranges) are based on the normal limits as defined in the Section [16.2.10] of the European PDT304 CSR.

Incidence rates for changes from baseline to follow-up (decrease, within, increase) for the following pre-specified magnitudes were produced:

Systolic BP: 20 mm-Hg

Diastolic BP: 10 mm-Hg

PR: 10 bpm

If any of these 3 parameters showed a change higher than the specific amounts, an additional table was generated.

Appropriate incidence rates of clinically notable abnormalities as defined in Section [16.2.10] of the European PDT304 CSR, were provided for all parameters in the same tables as for the changes regarding pre-specified changes.

Therefore, there were 3 descriptive analyses of vital signs describing any mentionable change from baseline to follow-up examination: shift tables for values outside the reference ranges (normal limits), tables for values outside pre-defined amounts changes, and tables for clinically notable abnormalities.

A by-subject listing of all vital signs (clinically notable abnormalities being flagged) was generated.

(e) Electrocardiograms

12-lead ECGs were recorded and evaluated at screening and at the 24- to 72-hour post injection follow-up visit. Any clinically significant abnormalities were recorded and described. ECGs were not recorded following the second injection of DaTSCAN™, nor planned for following the third injection. The ECGs were reviewed by the investigator for any occurrence of abnormal rhythm changes from baseline.

(f) Physical examinations

Physical examination status at each time point as well as changes from normal at baseline to abnormal at post-administration time point were presented for each centre using counts and percentages for the following parameters: general appearance, respiratory tract, urogenital system, cardiovascular system, gastrointestinal system, nervous system, musculoskeletal system, skin, hematological system and lymph nodes, and endocrine system.

(g) Injection site monitoring

Injection site reactions were not specifically collected in this study but such reactions were collected within the scope of AEs.

9.7.2 Determination of sample size

Originally, the study was planned for a period of 3 months and a total of 71 subjects (including 3 healthy volunteers) were enrolled into this 3-month study (subject numbers 01-0001 to 02-0081). As a consequence of amendment 4 (see Section 9.8.1.4), which included the extension of the study from 3 to 36 months, the sample size was recalculated and 131 additional subjects were included.

As per amendment 4, the sample size determination with respect to the final analysis at T = 36 was based on the parameters PPV and NPV and on 2 groups of subjects.

Group 1 (Probable PD):

Using a 95% 1-sided confidence interval (CI) and assuming 85% expected PPV, 35 abnormal scans were needed to estimate the PPV to within 10 percentage points. Assuming only 90% of all scans in Group 1 are actually abnormal and a 37% dropout rate, 62 subjects were to be recruited in Group 1.

Group 2 (Possible PD):

Using a 95% 1-sided CI and assuming 85% expected NPV, 35 normal scans were needed to estimate the NPV to within 10 percentage points. Assuming only 60% of all scans in Group 2 were actually normal and a 50% dropout rate, 118 patients were to be recruited in Group 2.

These sample size calculations ensured that Group 1 subjects provided an adequate number of abnormal subjects and Group 2 subjects provided an adequate number of normals for the resulting PPV and NPV estimates. The actual PPV and NPV estimates were based on the entire study population.

Thus, a total of 180 evaluable subjects were required to analyze the primary endpoint at T = 36 months.

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Main clinical study protocol

The main clinical study protocol (16 November 1998) was amended 10 times. All amendment summaries and the final protocol incorporating these amendments are included in Section [16.1.1]. Abstracts of all 10 protocol amendments are provided below.

9.8.1.1 Amendment 1 (21 December 1998)

To assess safety, collection of AE data for up to 7 days post-injection was determined to be adequate because of the very short half-life of the IMP. However, any ongoing AEs that had not resolved at the 7-day follow-up visit were to be reviewed at the 3-month follow-up visit.

9.8.1.2 Amendment 2 (01 July 1999)

(1) It was clarified that urinalysis laboratory safety data were to be collected from the start of the study.

(2) It was clarified that a thyroid-blocking protocol was to be followed according to local practices, not necessarily the agent specified in the final study protocol.

(3) The assessment of AEs/SAEs was updated.

9.8.1.3 Amendment 3 (04 October 1999)

(1) It was clarified that an additional biochemistry laboratory parameter (i.e., urea) was collected (starting on 01 September 1999).

(2) Starting on 01 October 1999, the expiry time on the day of calibration for the IMP was reduced from 12 to 7 hours post-calibration. Therefore, the labeling was updated. This change did not affect the imaging visit of the subjects.

(3) Additional confidence data given to the clinical impression at screening and at 3 months was collected

9.8.1.4 Amendment 4 (14 August 2000)

To meet post-authorization commitments to the Committee for Medicinal Products for Human Use (CHMP), the clinical study protocol was amended extensively. A summary of the major changes is given below:

(1) Study duration was extended to 36 months to monitor disease progression. Changes in DaTSCAN™ uptake were to be evaluated at 18 and 36 months compared to uptake after the first injection. Study objectives and efficacy endpoints were amended accordingly.

(2) The sample size was recalculated to increase the number of subjects: instead of 60 subjects included in the original 3-month study, a total of 180 subjects were required for the 36 months study.

(3) All subjects with features of early Parkinsonism were to return to the study center for a 3-month clinical assessment (F2 V4).

(4) Eighteen months and 36 months after the first injection, subjects were requested to return to the study center (S2 V5 and S3 V7, respectively) for screening. Assessments were to comprise: a check for protocol compliance; an assessment of disease status (UPDRS [part III] and H&Y); a video assessment of disease status; a pregnancy test for female subjects of child-bearing potential, and reporting of any AEs that may have occurred before the visit. In addition, subjects may have undergone a challenge test with apomorphine or levodopa to determine their response to therapy.

(5) Additional DaTSCAN™ injections/SPECT imaging were to be performed at 18 and 36 months (I2 V6 and I3 V8, respectively). These were to follow the same procedures as outlined for the first injection. Before each additional injection, a clinical study protocol compliance check was to be performed, resting vital signs were to be measured, and signs or symptoms recorded. Results of a pregnancy test for female subjects of child-bearing potential had to be known and negative prior to administration of DaTSCAN™ at each imaging visit. After SPECT imaging subjects were to be assessed for AEs and have their resting vital signs measured. A telephone interview was scheduled 7 days after each imaging visit (T2 and T3).

(6) The degree of confidence in a subject's diagnosis of idiopathic PD was to be provided by the investigators at screening (S1 V1), the 3-month follow-up (F2 V4), 18-month screening visit (S2 V5), after the 18-month imaging visit (I2 V6), 36-month screening visit (S3 V7), and after the 36-month imaging visit (I3 V8).

9.8.1.5 Amendment 5 (12 April 2001)

(1) The number of study centers was increased to 5.

(2) The age range of subjects who could be recruited was increased to 30-90 years (previously 30-80 years).

(3) An exclusion criterion was added: Subjects with a known, high sensitivity to iodine were to be excluded from the study.

(4) To assist with the assessment of images at the end of the study, the nuclear medicine physician at each center produced a set of images using a phantom supplied by the sponsor.

(5) The assessment of SAEs was updated.

9.8.1.6 Amendment 6 (27 June 2001)

All subjects with features of early Parkinsonism were to be video-taped at T = 0 as part of their screening assessments. In the event of a 36-month video not being performed for any reason, a baseline video should be available for comparison with the 18-month data.

9.8.1.7 Amendment 7 (07 December 2001)

(1) The instructions for SAE reporting were updated in line with sponsor policy.

(2) Post-menopausal female subjects were required to have been so for at least 2 years before they could enter the study without requiring a pregnancy test before DaTSCAN™ injection.

9.8.1.8 Amendment 8 (01 August 2002)

Reference to clinical safety officer details was changed.

9.8.1.9 Amendment 9 (29 April 2004)

(1) A preliminary analysis of the baseline data including the time point T = 18 months was added. The clinical study protocol was modified to incorporate the endpoints of this analysis.

(2) It was determined how to classify the diagnoses established by the MDS as a result of the independent video assessment as either PD or non-PD for subsequent efficacy analysis.

9.8.1.10 Amendment 10 (25 August 2005)

(1) The SOT was modified since a preliminary analysis of the 18-month follow-up data of the PDT304 study revealed some limitations of the video-based clinical assessment as the SOT. To increase the robustness of this procedure for the final analysis, a second MDS additionally analyzed the video data and established a diagnosis according to the same procedures followed by the first independent video reader. In case a diagnosis established for the T = 36 video data differed between the readers, they re-evaluated the mismatch together to come to a consensus diagnosis which was then used as the SOT for the respective subject.

(2) The primary efficacy endpoint was modified for 2 reasons: first, an independent SPECT read of DaTSCAN™ images was introduced after amendment 4 and the findings were included in the analysis. Second, PPV and NPV are dependent upon the distribution of PD and non-PD cases in the study population. Since these groups were highly unbalanced, PPV and NPV were of low relevance in this study. Therefore, sensitivity, specificity, and accuracy were added as additional parameters.

(3) It was decided not to perform the semi-quantitative analysis of the DaTSCAN™ images to assess for intra-individual disease progression for a number of reasons: the PDT304 study was originally redesigned to accommodate post-approval commitments agreed with the CHMP, which did not include semi-quantitative and/or progression analysis. It is known today that, even when only 1 gamma camera is used, a reliable assessment of intra-individual disease progression with dopamine transporter imaging is only possible if image acquisition is highly standardized, but in the present study neither phantom calibration nor strict adherence to set acquisition protocols across cameras was mandatory. Furthermore, there are no reports in the literature on the comparability of progression data across different cameras and/or centers. Additionally, it was not possible to reconstruct image data from all centers using the software required for semi-quantitative analysis.

(4) Three additional secondary endpoints were introduced:

- An endpoint to analyze for changes in DaTSCAN™ SPECT findings over time was included.
- Sensitivity, specificity, accuracy, NPV, and PPV for the independent SPECT readers at T = 0 compared to the on-site clinical diagnosis at T = 18 and T = 36 were analyzed.
- Since an independent SPECT read was added by amendment 4 and a second video reader was added by amendment 10, inter-reader agreement (for DaTSCAN™ SPECT readers and for independent video readers) was added as an endpoint.

(5) Secondary endpoints introduced for the T = 18 preliminary analysis (amendment 9) were extended to include the T = 36 time point.

(6) According to the original study protocol, the study population was to be divided into 2 groups based on the UK brain bank criteria: group 1 included subjects who fulfilled step 1 Brain Bank criteria; group 2 included subjects who did not fulfill step 1 Brain Bank criteria. This division was not conducted in this manner, since it is more appropriate to group subjects on the basis of the presence or absence of Parkinsonian symptoms.

(7) The concept of performing all analyses both for the per-protocol (PP) population and for the ITD population was changed to account for only 1 efficacy population. The originally planned ITD analysis was not feasible since more than half of the subjects withdrew from the study over the course of the trial and thus a SOT video assessment was often not available.

9.8.2 IIE protocol amendments

9.8.2.1 IIE protocol amendment 1 (29 April 2004)

The list of validated CRF data provided to the MDS in addition to the video-taped neurological assessments was modified as follows:

(1) The subjects' previous clinical diagnoses were deleted from the list and were not provided to the reader.

(2) A list of the medication recorded on the CRF was provided to the MDS.

9.8.2.2 IIE protocol amendment 2 (06 June 2005)

(1) An interim analysis of the 18-month data showed limitations of the video-based clinical assessment used in arriving at a SOT diagnosis (see main protocol amendment 10). Therefore, the procedures performed by the independent readers as described in the IIE protocol were modified accordingly and a separate consensus CRF was created.

(2) The video read CRF for the T = 36 video assessment was modified to allow for the documentation of a difference between the diagnosis established by the independent video reader at the T = 36 video assessment and the diagnosis established by the same reader at T = 18.

(3) The information provided to the readers along with the video-taped neurological assessments was modified to include whether the subject was right or left handed and whether the subject was in the off-phase of his/her dopaminergic medication.

(4) It was decided not to perform the semi-quantitative progression analysis as part of the final analysis for reasons discussed earlier (see main protocol amendment 10).

9.8.3 BIE protocol amendments

9.8.3.1 BIE SPECT protocol amendment 1 (25 August 2005)

Since it was decided not to perform the semi-quantitative analysis of the DaTSCAN™ images to assess for intra-individual disease progression (refer to main protocol amendment 10, Section [16.1.1]), BIE procedures related to semi-quantification were no longer required.

9.8.4 CRF Amendments

In addition to the above main protocol amendments, the on-site CRF was amended 3 times. A CRF based on the latest amendment is included in Section [16.1.2]. A summary of the main points of all 3 CRF amendments is provided below.

9.8.4.1 CRF amendment 1 (08 January 1999)

Minor changes only: typographical error was corrected.

9.8.4.2 CRF amendment 2 (01 July 1999)

The CRF was supplemented by urinalysis laboratory parameters that were collected by means of the laboratory analysis report for all subjects included to this date but had accidentally been omitted on the CRF page.

9.8.4.3 CRF amendment 3 (07 October 1999)

(1) The CRF was supplemented by an additional biochemistry laboratory parameter that had been collected from 01 September 1999 onwards.

(2) Additional data on the COD regarding the diagnosis of idiopathic PD was to be collected.

9.8.5 Changes to the Statistical Analysis Plan for the US Revision of the Clinical Study Report

The calculation of both diagnostic parameters was done over all probable PD subjects and non-PD subjects enrolled in the study for whom a SOT was available. Subjects with possible PD (as defined by the SOT diagnosis) were analyzed in secondary endpoints.

In the original, European CSRs, the primary objective was stated to the predictive value, and the primary endpoint was stated to be sensitivity, specificity, accuracy, PPV, and NPV for a) the on-site SPECT read and b) the independent SPECT BIE readers at T = 0 compared to the clinical diagnosis established by 2 independent MDS in consensus, based on the assessment of a video taken at T = 36 (Section [11.3.2.1] of the European PDT304 CSR). However, the study was powered based on assumptions around PPV and NPV (Section [9.7.2] of the European PDT304 CSR).

Given the assumptions around PPV and NPV (85% each, with sample sizes of 35 TP and TN subjects calculated to be needed for each) the corresponding expected values of FP and FN would each be calculated to be 6 subjects. From these expected values of TP, TN, FP, and FN, the expected values of sensitivity and specificity can be calculated, and would each be equal to the assumed PPV and NPV (i.e., 85%). Thus, had the study been powered based on sensitivity and specificity, the sample sizes would have been the same.

In the reanalysis for the US CSR, sensitivity and specificity for the detection or exclusion of a SDD are the primary objectives and will therefore be the focus of discussion. PPV and NPV will be reported solely because they were the original endpoints used to power the study; however sensitivity and specificity are considered better indicators of the intrinsic value of a diagnostic test (because they do not depend on the prevalence of the abnormality or disease of interest, as do PPV and NPV), and are considered of greater interest to regulatory authorities. To allow calculation of sensitivity and specificity, the assessment of each blinded image reader in assessing whether a subject's DaTSCAN™ image was abnormal or normal was compared to the SOT diagnosis to determine if the image assessment was a true or false positive or negative. A diagnosis of probable PD was taken to indicate the presence of a SDD, and a diagnosis of non-PD was taken to indicate the absence of a SDD (no SDD). The clinical diagnosis was established by 2 independent physicians who reviewed videotaped neurological examinations of subjects conducted after 36 months of follow-up (interim examinations were conducted after 18 months of follow-up also). The expert clinical diagnosis established at 36 months was used as the SOT. Subject groups were defined as:

(1) Probable PD

(2) Possible PD

(3) Non-PD (e.g., subjects with ET)

(4) Other

Sensitivity and specificity of the visual image analysis results for detecting or excluding a SDD were determined for the following comparisons:

(1) Probable PD vs non-PD;

(2) Possible or probable PD vs. non-PD; and

(3) Probable PD vs. Possible PD or non-PD.

Sensitivity and specificity (for detecting or excluding a SDD) were determined for each SPECT BIE reader as well as for the on-site DaTSCAN™ read; exact 95% CIs were used to summarize the diagnostic parameters. These endpoints were also determined for the on-site clinical diagnosis at T = 0 (pre-DaTSCAN™).

All of the above comparisons were done separately for the T = 36 SOT evaluations and for the PP and ITD study populations at each of the read time points (T = 0, T = 18, and T = 36).

In addition, the sensitivity and specificity of the visual image assessments and the on-site clinical diagnosis at baseline and at T = 18 were determined using as the SOT the clinical diagnoses established by each video reviewer at T = 18; the results were reported for each video reader and the mean sensitivity and specificity for the 3 BIE readers and the 2 video reviewers were also reported.

9.8.5.1 Data conversion for CDISC compliance

This is described above in Section 9.6.

9.8.5.2 Clinical study report integration

Originally, there were 2 European CSRs, one for the interim analysis (after the 18-month follow-up), and one final report which reported the integrated interim and final results after the 36-month follow-up. In support of a US NDA submission, this CSR was prepared using data from both CSRs combined. The discussion in this CSR is focused on endpoints that are considered of greatest clinical and/or regulatory relevance. This resulted in a simpler presentation of the results that will be easier to review.

9.8.5.3 Statistical analysis plan

The statistical analysis plan that was followed for the US CSR is appended in Section [16.1.9].

The statistical analysis plan for the US CSR and this report do not include all of the analyses specified in the study protocol. Results for the analyses not specified here can be found in the European PDT304 CSR.

Tabulations of summary statistics, graphical presentations, and statistical analyses were performed using SAS® Software (Version 9.0).

All continuous variables were summarized by the following descriptive statistics: number of subjects (N), number of subjects in a subgroup (n), mean, standard deviation (SD), median, minimum (Min), maximum (Max). Discrete variables were summarized by counts and percentages. Other parameters were tabulated as appropriate.

Disposition of Subjects:

The following information on subject disposition was provided:

- Number of subjects enrolled.
- Number of subjects who received DaTSCAN™ (i.e., who were dosed).
- Number of subjects included in the safety analysis.
- Number of subjects included in the efficacy analysis (PP and ITD).

Completion status was tabulated, together with reason(s) for non-completion and reason(s) for withdrawal.

Summaries of demographic data were also done for the safety population overall and by SOT diagnosis.

Medical history is not addressed in this document. A summary of the subjects' medical history can be found in the European PDT304 CSR.

Previous and concurrent medications are not addressed in this document. A summary of the subjects' prior and concurrent therapy or medication can be found in the European PDT304 CSR.

Parameters relating to dosing and administration of DaTSCAN™ are not addressed in this document. A summary of test article administration can be found in the European PDT304 CSR.

Protocol violations were not addressed specifically for this US CSR. A brief summary of protocol violations as reported in the European submission can be found in Section 10.2 of this CSR. A complete discussion of protocol violations can be found in the European PDT304 CSR.

No exploratory analyses were performed for the US CSR.

9.8.5.4 Definition of study populations

The ITD population was defined in the protocol as all subjects recruited, who had at least 1 dose of DaTSCAN™ and who completed a SPECT imaging.

The PP population was defined in the protocol as the subset of the ITD population. This subset of subjects would exclude data for subjects who violated the following criteria:

- Subject elected to withdraw from the study for reasons other than experience of AEs.
- Lack of co-operation with study requirements.
- Subject did not comply with the inclusion/exclusion criteria.
- Use of prohibited concomitant medication between screening and the imaging phase of the study, and/or during the imaging phase of the study.
- SPECT imaging performed outside the acceptable validation range for DaTSCAN™ imaging, i.e., less than 3 hours and more than 6 hours post-injection.
- Subject did not receive 111–185 MBq of DaTSCAN™.

For this CSR, the ITD and PP populations were defined as follows:

(a) Intent-to-diagnose (M18 ITD or M36 ITD) population

A subject was part of the Month-18 and/or Month-36 ITD population if both the baseline DaTSCAN™ SPECT imaging assessment was performed and the clinical diagnosis (SOT) based on the Month-18 or Month-36 video assessment, respectively, was established by 2 independent MDS. An exception was made for the 3 healthy volunteers: although no Month-36 video assessment was performed they were included in the efficacy population and were considered to be non-PD subjects with respect to subsequent analysis.

(b) Per-protocol (M18 PP or M36 PP) population

Subjects considered for the PP population included subjects in the respective Month-18 or Month-36 ITD populations with no major protocol deviations. All protocol deviations were discussed within the study team on a case-by-case basis during a data review meeting held on 26 October 2005. Subjects listed with a major deviation are listed in Section 10.2.

(c) Safety population

Subjects considered for this population included subjects who received any amount of DaTSCAN™ and underwent at least 1 safety assessment.

9.8.5.5 Data conventions

(a) Handling of dropouts and missing data

No imputation was done for missing data.

(b) Pooling of investigator sites

Data from all investigator sites was combined for analysis.

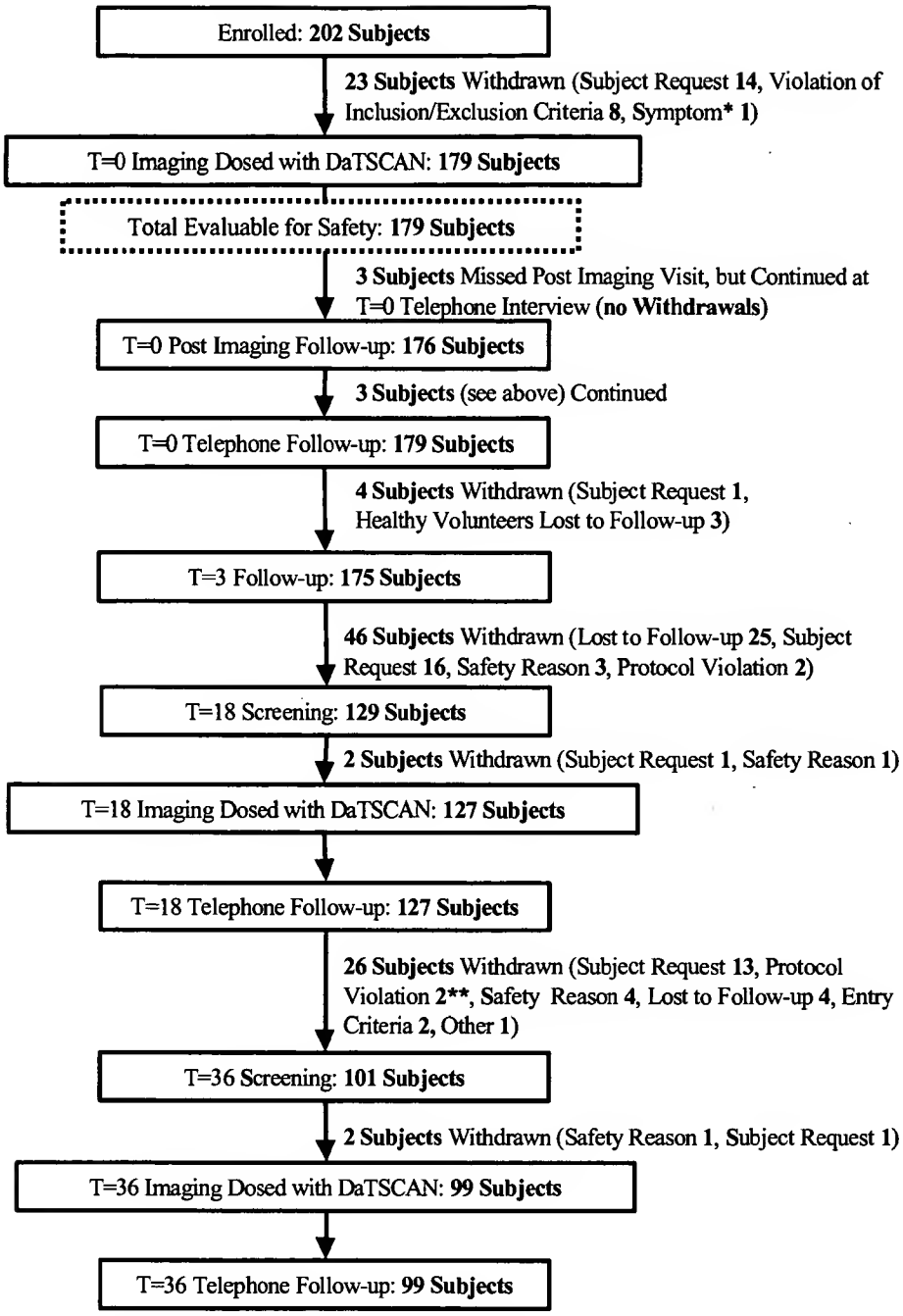
10 STUDY SUBJECTS

10.1 Disposition of Subjects

In total, 202 subjects were enrolled into the study. Of these, 179 were dosed at T = 0, 127 were dosed at 18 months (T = 18) and 99 were dosed at 36 months (T = 36). In total, 102 subjects were included in the ITD population and evaluable for primary efficacy analysis, and 179 were included in the Safety Population.

Figure 5 illustrates the disposition of subjects.

Figure 5 Disposition of Subjects



* Withdrawal was recorded in CRF as "Withdrawn due to an Adverse Event", but since the event occurred before dosing it was classified as a symptom for the purpose of this analysis.
** A total of 3 subjects were listed as withdrawn due to protocol violation for this time point; however 1 subject (01-0002) continued and was therefore included in the safety/efficacy populations where possible.

Before the first DaTSCAN™ administration at T = 0, 23 subjects were withdrawn from the study. The reasons were: 1 subject was withdrawn because of the occurrence of a pre-treatment symptom (recorded as an "AE" in the database), 8 subjects due to a violation of an inclusion or exclusion criterion noticed after performing laboratory and neurological evaluations at screening, and 14 subjects elected to withdraw. As these 23 subjects did not receive DaTSCAN™, they were not included in the safety population.

Of the 179 subjects dosed with DaTSCAN™ at the T = 0 imaging visit, 52 withdrew before the second dosing at T = 18.

Of the subjects enrolled into the original 3-month study, 28 subjects (25 subjects plus 3 healthy volunteers) completed the 3-month visit but did not re-enter the study for any further study procedures. They were categorized as "lost to follow-up".

- 18 subjects elected to withdraw after dosing.
- 4 subjects did not complete the study due to safety-related reasons.
- 1 subject experienced an AE.
- 3 subjects experienced SAEs with fatal outcome. These AEs were considered to be unrelated to DaTSCAN™ by the investigator (see also Sections 12.1 and 12.2).
- 2 subjects were withdrawn after the first dosing due to protocol violations (see also Section 10.2).

At the T = 18 imaging visit, 127 subjects were still in the study and received DaTSCAN™ a second time.

After the second dosing, 28 subjects withdrew from the study and 99 subjects were dosed with DaTSCAN™ a third time during the T = 36 imaging visit. The reasons for the withdrawals were:

- 4 subjects were lost to follow-up after the T = 18 telephone follow-up visit.
- 14 subjects elected to withdraw.
- 5 subjects were withdrawn because of AEs, of which one subject experienced an AE with fatal outcome.
- 2 subjects declined video-taping of neurological assessments at T = 18, and were excluded from the study due to this protocol violation after having completed the T = 18 telephone follow-up visit.
- 1 subject was discontinued from the study because the investigator judged the subject not suitable for further SPECT imaging for medical reasons.

- Subject 01-0002 refused video-taping during the T = 36 screening visit and was therefore reported as discontinued from the study due to a protocol violation (CRF page 138). However, the subject continued to participate in the study and completed all visits including the T = 36 telephone follow-up. Therefore, the study population at T = 36 included subject 01-0002 and comprised 99 subjects. Tables and listings referring to the study completion statement do not include subject 01-0002 and comprise 98 subjects.

For further information on subject discontinuation see Sections 14.1, Tables [14.1.1] to [14.1.4.5] and Section [16.2] of the European PDT304 CSR. Table 11 summarizes the numbers of subjects enrolled, dosed, discontinued from the study, and evaluable for safety and efficacy.

Table 11 Subject Disposition

Disposition	**N**
Total enrolled	202
Withdrawn prior to first dosing	23
Subject request	14
Subject excluded	8
Safety reason	1
Dosed at baseline	**179**
Withdrawn after baseline and before the 18-month dosing	52
Lost to follow-up	25
Healthy volunteers lost to follow-up	3
Subject request	18
Safety reason	4
Protocol violation	2
Dosed at 18 months	**127**
Withdrawn after 18-months and before the 36-month dosing	28
Lost to follow-up	4
Subject request	14
Safety reason	5
Protocol violation[a]	2
Subject excluded	2
Other	1
Dosed at 36 months	**99**
Study completers[a]	98
Evaluated in the Baseline SPECT BIE	174
Evaluated in the 18-month IEE Video Assessment	
Reader 1	128
Reader 2	125
Evaluated in the 36-month Consensus IIE Video Assessment[a]:	102
M18 ITD population	128
M18 PP population	124
M36 ITD population	102
M36 PP population	100
Total Evaluable for Primary Efficacy Analysis[a]	102

N = number of subjects for respective category; BIE = blinded image evaluation; IE = independent evaluation (consensus panel).
ITD = Subjects who underwent SPECT imaging after receiving DaTSCAN™ and underwent the respective 18-month or 36-month SOT assessment.
PP = Subjects in the ITD population with no major protocol violations.
[a] Subject 01-0002 counted as non-completer in the end of study statement, however, the subject completed all T = 36 visits and is included in safety/efficacy populations.
REF: Section 14.1, Table [14.1.1]

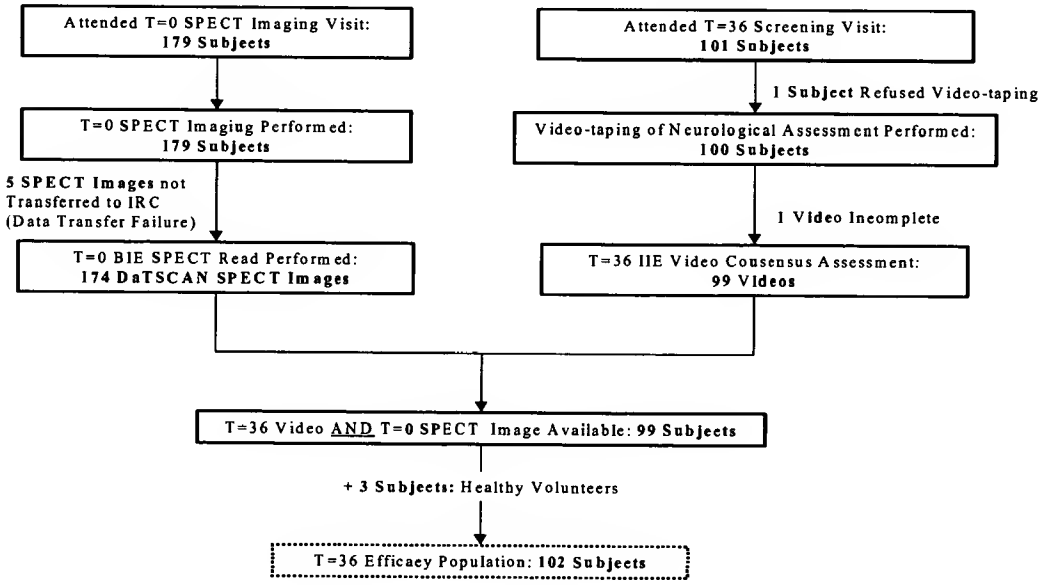
The decision as to the inclusion or exclusion of a subject in the efficacy evaluation was based on the following criteria: a subject was considered evaluable for efficacy analysis if both a 1) T = 0 DaTSCAN™ SPECT image and 2) T = 36 video of neurological assessments had been evaluated as part of the corresponding independent reads. The T = 36 IIE video assessment was conducted to classify subjects as either PD or non-PD. Since the healthy volunteers were considered to be non-PD subjects without any additional assessments aside from screening examinations, the only prerequisite for healthy volunteers for inclusion in the efficacy population was having an evaluable T = 0 DaTSCAN™ image.

At T = 0, 179 subjects underwent DaTSCAN™ SPECT imaging. Due to file transfer failure from center 03 to the IRC, 5 DaTSCAN™ SPECT images could not be evaluated in the T = 0 SPECT read. These 5 subjects (03-0300, 03-0303, 03-0305, 03-0306, 03-0308) were withdrawn from the study before video-taping at T = 36.

A total of 101 subjects attended the T = 36 screening visit, in which the video-taping of the neurological assessments was performed. However, a consensus diagnosis based on the independent video assessment was available for a total of only 99 subjects: 1 subject (subject 01-0002) refused to be video-taped. Due to incompleteness of neurological assessments, the videotape was considered to be non-evaluable by 1 of the independent video readers for subject 01-0124.

Figure 6 shows the allocation of the subjects to the primary efficacy population. Additional efficacy populations for the secondary efficacy evaluation are described in Section 11.1.

Figure 6 Disposition of Efficacy Population



10.2 Protocol Deviations

The protocol deviations that occurred during this study were grouped in the following categories:

(1) Subjects who violated the study entry criteria and were withdrawn.

(2) Subjects who violated the study entry criteria but were not withdrawn.

(3) Subjects with deviation from the order of study procedures.

(4) Subjects with deviation from the timeframe of study procedures.

(5) Subjects with deviation from the procedure of recording radioactivity injected.

(6) Subjects who received commercial DaTSCAN™ instead of IMP.

(7) Subjects with missing or incomplete video assessment.

(8) Administered radioactivity outside range.

(9) Subject not in medication off-phase during video taping.

(10) Subject received prohibited concomitant medication.

All protocol deviations were discussed within the study team on a case by case basis during a data review meeting held on 26 October 2005. A total of 181 protocol deviations were reported for 93 subjects. The majority of the protocol deviations (160, 88.4%) were classified as minor; 21 (11.6%) deviations were classified as major.

Protocol violations by center are presented in Section [16.2.2] in the European PDT304 CSR. An overview of the inclusion/exclusion criteria can be found in Section [16.2.2] of the European PDT304 CSR.

Table 12 summarizes the protocol deviations reported during this study.

Table 12 Protocol Deviations

Subject Number	Type	Actual Deviation	Action Taken	Grade
01-0133, 01-0121	(1)	Violation of Exclusion Criterion 17 (increased lab value)	Withdrawn before dosing, excluded from efficacy and safety population	Major
01-0005, 01-0007, 01-0035, 01-0107, 01-0136, 04-0408	(1)	Violation of Inclusion Criterion 04 (UPDRS score >16)	Withdrawn from further study procedures, excluded from efficacy and safety population	Major
01-0101	(1)	Violation of Inclusion Criterion 04 (UPDRS score >16)	Withdrawn from further study procedures, excluded from efficacy, included in safety population	Major
01-0140	(1)	Violation of Exclusion Criterion 15 (i.e., participation in another study)	Withdrawn from further study procedures and excluded from efficacy, included in safety population	Major
06-0616	(2)	Violation of Exclusion Criterion 06 (prohibited concomitant treatment)	Subject elected to withdraw at T = 0 screening visit; excluded from efficacy and safety population	Major
06-0618	(2)	Violation of Exclusion Criterion 15 (participation in another study)	Included in efficacy and safety population	Minor
01-0038	(2)	Violation of Inclusion Criterion 04 (UPDRS score >16)	Included in safety and efficacy population	Minor
06-0603 (06-1603), 06-0604 (06-1604)	(3)	2 T = 0 imaging visits performed	Included in efficacy and safety population	Minor
07-0700	(3)	Subject had 2 screening visits, 1 was entered in the database	Included in efficacy and safety population	Minor
01-0102, 06-0603, 06-0604	(3)	Subject missed T = 0 follow-up visit	Included in safety and efficacy population	Minor
02-0051, 02-0069	(4)	Time between DaTSCAN™ injection and beginning of imaging outside range	Included in safety and efficacy population	Minor
05-0500 to 05-0528	(5)	Radioactivity after injection not measured	Included in safety and efficacy population	Minor
01-0002, 01-0004, 01-0058, 02-0063	(6)	Subject received commercial DaTSCAN™	Included in safety and efficacy population	Minor
01-0002, 01-0016, 01-0028, 01-0033	(7)	Subjects declined video-taping of neurological assessments	Excluded from efficacy analysis	Major
01-0124	(7)	Video assessment incomplete	Excluded from efficacy analysis	Major
10-1004	(7)	T = 18 video misplaced	Excluded from efficacy analysis	Minor
02-0201	(8)	Radioactivity administered 190.7 MBq	Included in safety and efficacy population	Minor
05-0526, 10-1005	(9)	Subject not in off-phase during video-taping	Included in safety and efficacy population	Minor
01-0031, 02-0081, 06-0603	(10)	Prohibited concomitant medication (sertraline)	Included in safety and efficacy population	Major

REF: Section [16.2.2] in the European PDT304 CSR.

A total of 10 subjects were withdrawn from the study due to major violations of the study entry criteria. Two of these violations occurred after the subjects' first dosing at T = 0, therefore these subjects were included in the safety population.

The protocol deviations that did **not** lead to withdrawal of a subject from the study are described in the following:

Subject 06-0618 participated in another clinical study involving the administration of an unlicensed radiopharmaceutical drug. As half-life elimination of this drug was less than 24 hours and the administration date 1 month before the T = 18 screening visit, the investigator decided not to withdraw the subject from any further study procedures.

For subject 01-0038 a UPDRS score of 17 was assessed at T = 0 screening. As categorization of subjects is affected by individual clinical judgment, a deviation of 1 score point from the prescribed maximum value of 16 scores was considered to be tolerable and did not lead to the exclusion of the subject from the efficacy population.

SPECT imaging at T = 0 of subjects 06-0603 and 06-0604 had been performed, but image data were not available as it had been misplaced at the investigational site. For both subjects, a second imaging visit was scheduled and performed. All data collected in the CRF during the "first" T = 0 imaging visit, the T = 0 post-imaging follow-up and the T = 0 telephone follow-up were re-entered into the database as separate subject numbers (06-1603, 06-1604) and listed accordingly, but not tabulated. Data captured during the respective "second" T = 0 imaging visit and T = 0 telephone follow-up was entered in the database as the data evaluable for subjects 06-0603 and 06-0604, i.e., listed and tabulated. Data for the T = 0 post-imaging follow-up was not available for as it was not performed a second time. The protocol deviations for subjects 06-0603 and 06-0604 are described in 2 notes to the file (20 November 2002, 17 December 2002).

Subject 07-0700 attended 2 screening visits, 1 on 09 October 2001, and another on 13 March 2002. The subject was withdrawn after the first screening visit due to a high leukocyte value. After the value had returned to normal, the subject was re-screened on 13 March 2002 and participated in the study without being assigned a new study allocation number. Only the second screening visit was entered in the database. Details are described in a note to the file (21 November 2002).

Subjects 01-0102, 06-0603, 06-0604 missed the T = 0 post-imaging follow-up visit for unknown reasons. All other visits were completed; therefore the subjects were kept in the study and included in the efficacy and safety population.

T = 0 SPECT imaging of subjects 02-0051 and 02-0069 was performed 2:40 and 2:51 hours after DaTSCAN™ injection, which is slightly outside the given range of 3 to 6 hours. Both subjects were included in the efficacy evaluation.

Center 05 deviated from the prescribed procedure of calculating the total radioactivity injected for DaTSCAN™ imaging. According to the CRF, calculation of radioactivity was based on 2 values: the radioactivity present in the syringe prior to injection minus the radioactivity measured following the injection. All 3 values (i.e., radioactivity prior to injection, following

injection, and actual radioactivity injected) were to be entered in the CRF. At center 05 the value for the radioactivity present after DaTSCAN™ was not measured. For all subjects with missing values, the values measured prior to injection were entered as total radioactivity injected. All of the subjects were included in the safety and efficacy population.

Although subjects 01-0002, 01-0004, 02-0058, and 02-0063 received commercial DaTSCAN™ instead of study drug erroneously during the T = 18 imaging visit, they were included in both the efficacy and the safety population. The study drug is identical to the commercial DaTSCAN™; however, the investigators were advised to use only study drug for T = 36 imaging.

Six subjects had to be excluded from the respective efficacy population because of missing videos: subject 01-0002, declined video-taping of the neurological assessments at the T = 36 screening visit; subjects 01-0016, 01-0028, and 01-0033 declined video-taping of neurological assessments at the T = 18 screening visit. For subject 01-0124 the neurological assessments on the T = 36 video were incomplete and the video could therefore not be evaluated. Subject 10-1004 was video-taped at T = 18, but the video was misplaced at the investigational site.

For subject 02-0201 the radioactivity administered during the T = 36 imaging visit was 190.7 MBq and hence above that recommended in the current Summary of Product Characteristics (range of 111 to 185 MBq). However, the radioactivity administered was still less than the upper range of 250 MBq specified for DaTSCAN™ in the guidelines of the European Association of Nuclear Medicine [Tatsch et al. 2002]. No AEs were reported for the subject during the follow-up period of the study. The protocol violation was classified as minor and the subject included in the safety and efficacy population.

Subjects 05-0526 and 10-1005 were not in the off-phase of anti-Parkinsonian medication during video-taping of neurological assessments at T = 36. Since the independent video readers were supplied with this information and considered both subjects as being evaluable they were not excluded from the efficacy population.

Agents with high affinity for DaT such as amphetamine, benzatropine, buproprion, cocaine, mazindol, methylphenidate, phentermine, and sertraline are identified as having interaction potential with DaTSCAN™ and were therefore prohibited in the study. Three subjects (subjects 01-0031, 02-0081, and 06-0603) were administered sertraline during their participation in this study. However, for all possible drug effects which could theoretically result in higher or lower overall striatal binding of DaTSCAN™, interactions are expected to be uniform and not asymmetrical and are not expected to result in a change in putamen/caudate ratios. Thus, visual assessment of the DaTSCAN™ image which is based on defined patterns should not be affected with regard to the decision as to whether the image is normal or abnormal. Therefore, despite being classified as major protocol violators, all 3 subjects remained in the safety and efficacy populations.

The protocol deviations listed and described above did not have an impact on the study results.

10.3 Demographic and Other Baseline Characteristics

10.3.1 Demographic characteristics

At T = 0, 179 subjects were dosed. A slightly higher percentage of the subjects were male (57% vs. 43%). All 179 subjects (100%) were Caucasian. Mean (SD) age was 61.6 (10.95) years; median age was 63.0 years and ranged from 33 to 86 years. Mean (SD) height was 168.6 (9.59) cm; median height was 168.0 cm and ranged from 144 to 198 cm. Mean (SD) weight was 73.19 (13.462) kg; median weight was 73.00 kg and ranged from 45.0 to 116.0 kg. Mean (SD) BMI was 25.75 (4.330) kg/m^2; median BMI was 25.15 kg/m^2 and ranged from 16.4 to 40.5 kg/m^2.

When displayed according to the subjects' SOT diagnosis the proportion of male subjects in the non-PD group was higher (68%) compared to that in the probable PD group (52%), consistent with the known demographics of PD. Table 13 presents the demographic characteristics by SOT diagnosis.

Table 13 Summary of Subject Demographics – Safety Population

Variable		Overall (N=179)	Standard of Truth Diagnosis (Month 36)			
			Probable PD (N=66)	Possible PD (N=5)	Non-PD (N=31)	No Diagnosis (N=77)
		n (%)	n (%)	n (%)	n (%)	n (%)
Gender n (%)	Male	102 (57)	34 (52)	2 (40)	21 (68)	45 (58)
	Female	77 (43)	32 (48)	3 (60)	10 (32)	32 (42)
Race n (%)	Caucasian	179 (100)	66 (100)	5 (100)	31 (100)	77 (100)
Age (Years)	Mean (SD)	62 (11)	61 (10)	69 (9)	57 (13)	63 (11)
	Min, Max	33, 86	43, 78	57, 79	33, 79	34, 86
	Median	63	61	67	58	64
Height[a] (cm)	Mean	169 (10)	167 (9)	165 (12)	171 (9)	169 (10)
	Min, Max	144, 198	144, 183	148, 180	151, 187	147, 198
	Median	168	167	168	170	170
Weight[a] (kg)	Mean	73 (13)	72 (13)	66 (13)	78 (14)	73 (13)
	Min, Max	45.0, 116.0	45.0, 103.0	49.0, 81.0	57.2, 116.0	47.5, 112.0
	Median	73	73	70	79	72
BMI[a] (kg/m^2)	Mean	26 (4)	26 (5)	25 (5)	27 (4)	25 (4)
	Min, Max	16.4, 40.5	17.6, 40.5	17.4, 31.2	20.7, 34.8	16.4, 38.1
	Median	25	26	25	27	25

N = number of subjects dosed; n = number of subjects with the respective demographic information; SD = standard deviation; PD = Parkinson's Disease; BMI = body mass index.
Percentages are based on the safety population.
Safety population includes all subjects dosed.
[a] Height and weight missing for 1 probably PD subject and 1 subject with no diagnosis.
REF: Table [14.1.2].

Detailed demographic characteristics can be found in Section 14.1 (Tables [14.1.5.1] to [14.1.5.4]), Section [14.1.6] and Section [16.2.4] of the European PDT304 CSR.

As the targeted study population was to be either early PD or ET, only subjects with a total UPDRS score of ≤ 16 were to be included in this study according to the inclusion/exclusion criteria. All but 1 subject included in the efficacy population at T = 0 were scored ≤ 16

(subject 01-0038, UPDRS score of 17, see details in Section 10.2). Additionally, to ensure inclusion of non-PD subjects, at least 30% of the subjects were to have a clinical rating score of ≤8 at study entry. A total of 70 subjects (41.2 % of the efficacy population) presented with a total UPDRS score of 8 or less at their first screening visit (see Section 14.2, Table [14.2.1.2.1] of the European PDT304 CSR).

The on-site UPDRS score for the total efficacy population increased over time: the mean UPDRS score increased from 10.0 at T = 0 screening to 16.1 at T = 36 screening (see Section [10.4.3] of the European PDT304 CSR). Analyzed by subgroups, the group of probable PD subjects showed the highest increase over the whole study period from a mean UPDRS score of 10.8 (T = 0) to 20.3 (T = 36), whereas the UPDRS score in the non-PD group remained stable over time (6.4 at T = 0; 7.1 at T = 36). The increase in mean UPDRS scores over time in the probable PD subjects (SDD subjects) is consistent with the known natural history of PD; it is a progressive condition in which symptoms and signs worsen over time, and this worsening is reflected in increased UPDRS scores. Conversely, the lack of increase in UPDRS scores in the non-PD group (non-SDD subjects) is consistent with the known lack of progression in non-PD conditions such as ET.

The on-site H&Y staging at screening also showed an increase over time from a mean value of 1.5 (T = 0) to 2.0 (T = 36) (see Section [10.4.3], of the European PDT304 CSR). Analyzed by subgroup, the group of probable PD subjects showed a noticeable increase from 1.5 (T = 0) to 2.2. (T = 36), whereas no significant change over time for the non-PD group could be observed (1.6 at T = 0; 1.7 at T = 36). The behavior of the H&Y scores was also consistent with the known natural history of the respective conditions. The increase in mean H&Y scores over time in the probable PD subjects (SDD subjects) is consistent with the known natural history of PD, and the lack of increase in H&Y scores in the non-PD group (non-SDD subjects) is consistent with the known lack of progression in non-PD conditions such as ET.

10.3.2 Neuropsychiatric characteristics

The neuropsychiatric characteristics of the study population are not addressed in this report. Section [10.4.3] of the European PDT304 CSR compared neuropsychiatric characteristics among early PD, ET, and non-PD subjects and did not find unexpected differences that could have affected study results.

10.3.3 Abnormal medical history

In total, 174 subjects (97.2%) reported prior medical/surgical history at T = 0 screening. The most common medical disorders reported were "surgical and medical procedures" (96 subjects, 53.6%), followed by "musculoskeletal and connective tissue disorders" (74 subjects, 41.3%), "vascular disorders" (48 subjects, 26.8%), and "psychiatric disorders" (43 subjects, 24.0%). All other body systems were affected in less than 40 subjects. Overall, there were no relevant differences between subject subgroups in the reported frequencies in medical history. Details on the occurrence of abnormal medical histories at study entry for subjects in the safety population, overall and by SOT diagnosis may be found in Section [10.3.2] of the European PDT304 CSR.

10.3.4 Prior or concurrent medication

Of the total safety population (N=179), 157 (87.7%) subjects were taking concurrent medication at study entry or up to 4 weeks prior to inclusion into the study. The most commonly administered medications were anti-Parkinson medication (33%), followed by analgesics (21.8%), beta-blocking agents (17.9%), psycholeptics (15.1%), and diuretics (14.5%). No major differences in medication administered were seen among subgroups.

Subjects taking medication known or suspected to affect striatal uptake of DaTSCAN™ were not to be included in the study (Section 9.4.10). This was adhered to in all but 3 subjects, who were taking sertraline (see Section 10.2). In each case, the investigator considered the subject's participation in the study of clinical benefit but considered the complete withdrawal of medication to be detrimental.

Details of the numbers and percentages of subjects taking concurrent medications at study entry for subjects in the safety population, overall and by SOT diagnosis may be found in Section [10.3.3] of the European PDT304 CSR.

10.3.5 Investigational medicinal product and dosage received

The numbers of subjects administered DaTSCAN™ were 179 at T = 0, 127 at T = 18, and 99 at T = 36. No major differences were seen between study drug administration characteristics at T = 0, T = 18, and T = 36. Radioactivity injected was within the range of 116 to 190.7 MBq, and was within the approved dose of 111 to 185 MBq for all but 1 subject. The subject (02-0201) is described in Section 10.2. The mean volume aspirated from vial for injection was 2.4 mL for all time points and corresponded to the maximum volume of 2.5 mL as specified in the clinical study protocol. A summary of information on DaTSCAN™ administration for all time points is presented in Section [10.4.1] of the European PDT304 CSR.

10.3.6 Procedural medication

In the present study each subject was to receive a thyroid blocking agent prior to DaTSCAN™ administration, according to the center's thyroid blocking protocol. At each imaging time point, each dosed subject received thyroid blocking prior to DaTSCAN™ administration. A second thyroid blocking after imaging was not required but was performed if deemed necessary by the investigator. Detailed information on thyroid blocking is listed in Section [16.2.2] of the European PDT304 CSR.

11 EFFICACY EVALUATION

11.1 Data Sets Analyzed

To identify minor and major protocol violations and to define the safety and efficacy population for analysis, blinded review study team meetings took place on the 26th and the 31st of October 2005. For details on the meetings please refer to Section [16.1.9] of the European PDT304 CSR. Protocol violations are listed and described in Section 10.2. The study population is presented in Figure 5 and Figure 6.

Intent-to-Diagnose (M18 ITD or M36 ITD) Population

The ITD population is defined in Section 9.8.5.4. The ITD population at T = 18 consisted of 128 subjects (including the 3 healthy volunteers). The ITD population at T = 36 consisted of 102 subjects (including the 3 healthy volunteers). The criteria for the determination of the ITD population and an overview of the allocation of subjects to the ITD population are given in Section 10.1. A total of 102 subjects were evaluable for the primary efficacy analysis (Table [14.1.1]).

Per-Protocol (M18 PP or M36 PP) Population

The PP population is defined in Section 9.8.5.4. The PP population at T = 18 consisted of 124 subjects (including the 3 healthy volunteers) (Table [14.1.1). The PP population at T = 36 consisted of 100 subjects (including the 3 healthy volunteers).

11.2 Measurements of Treatment Compliance

Subjects received DaTSCAN™ under direct supervision of study personnel. Radioactivity injected was independently checked and recorded in the CRF. The vial labels, containing subject number and vial number, were attached to the subject's CRF.

11.3 Efficacy Results and Tabulations of Individual Subject Data

11.3.1 Analysis of efficacy of DaTSCAN™

11.3.1.1 Standard of truth and other diagnoses

(a) Final SOT assessments (based on IIE and other clinical information at T = 36)

Analyses of sensitivity and specificity were based on the final (T = 36) SOT, i.e., the expert clinical diagnosis established by 2 independent MDS. This diagnosis was made on the basis of the MDS review of a video recording of a neurological examination conducted at T = 36 in combination with additional clinical information. The expert clinical diagnosis ("probable

PD", "possible PD", or "Non-PD") was used as an indication of whether or not the subject had a SDD: "probable PD" was taken to indicate the presence of a SDD; "Non-PD" was taken to indicate the absence of a SDD, and "possible PD" was taken into indicate a possible SDD.

A consensus meeting was held to re-evaluate the cases in which the 2 MDS differed in the diagnosis for a subject. This was the case for 18 subjects, which were re-evaluated to come to a final consensus expert clinical diagnosis. In total, a SOT diagnosis for T = 36 was established for 99 subjects.

Table 14 shows the final diagnosis after the consensus read meeting. After combining the diagnoses "probable PD" and "possible PD" into 1 category "PD," this diagnosis served as SOT for determining if the subject had a SDD or not. Additionally, 3 healthy volunteers took part in the study. They did not undergo the T = 36 video assessment. However, since the T = 0 DaTSCAN™ images were available, they were added to the efficacy population and coded as "non-PD." Therefore, for 102 subjects a final SOT assessment was available.

Table 14 Final Consensus SOT Assessments (Based on IIE and Other Clinical Information at T = 36)

Reader	N	MDS Diagnosis (SOT)		
		Probable PD (SDD) n (%)	Possible PD (SDD) n (%)	Non-PD (no SDD) n (%)
Final consensus assessment	102	66 (65)	5 (5)	31 (30)

N = Efficacy population for T = 36, including 3 healthy volunteers (classified as non-PD), although they did not undergo video assessment.
n = Number of subjects with respective diagnosis
REF: Section 14.2, Table [14.2.7.1].

The prevalence of a SDD was 66/102 (65%) if based on the prevalence of probable PD, and 71/102 (70%) if based on the prevalence of probable/possible PD.

A tabulation of the diagnoses established by each of the 2 readers independently after assessing the T = 36 videos is presented in Table [21] (Section 11.3.1) of the European PDT304 CSR.

(b) Interim SOT assessments (based on IIE and other clinical information at T = 18)

Statistical analysis of endpoints B and C used the diagnosis established by the 2 MDS (i.e., video readers) on the basis of the assessment of a video taken at T = 18 in combination with additional clinical information as the interim SOT. Table 15 summarizes the video reader diagnoses. No consensus meeting to re-evaluate mismatches was held at T = 18.

Table 15 Interim SOT Assessments (Based on IIE and Other Clinical Information at T = 18)

Reader N	MDS Diagnosis (SOT)		
	Probable PD (SDD) n (%)	Possible PD (SDD) n (%)	Non-PD (No SDD) n (%)
Reader 1 (N = 128)	89 (70)	11 (9)	28 (22)
Reader 2 (N = 128)	69 (55)	26 (21)	30 (24)

N = number of subjects evaluated; n = number of subjects in each category; PD = Parkinson's Disease. Includes 3 healthy volunteers (classified as non-PD) although they did not undergo video assessments.
NOTE: Subjects classified as "Benign PD" were tabulated as "Possible PD," and subjects classified as "Other" were tabulated as "Non-PD."
REF: Section 14.2, Tables [14.2.1.1.a] and [14.2.1.1.b].

For the ITD efficacy population of 128 subjects (including 3 healthy volunteers), reader 1 classified 89 (70%) subjects as probable PD, 11 (9%) subjects as possible PD, and 28 (22%) subjects as non-PD. For the same ITD efficacy population of 128 subjects, reader 2 classified 69 (55%) subjects as probable PD, 26 (21%) subjects as possible PD, and 30 (24%) subjects as non-PD. The results of an analysis of inter-reader agreement are reported in Section 11.3.1.3 (Secondary Endpoint H).

(c) On-site clinical diagnoses at T = 0, T=3, T = 18, and T = 36 screening

The sensitivity and specificity of the clinical diagnosis and the SPECT image reads were compared. Additionally, the on-site clinical diagnosis at T=3 before SPECT imaging served as the SOT for secondary endpoint A, and the on-site clinical diagnoses at T = 18 and T = 36 screening served as the SOT for secondary endpoint F.

Table [24] (Section 11.3.1.3) of the European PDT304 CSR presents the results of the on-site clinical diagnosis for the respective efficacy populations as established by the on-site neurologists.

(d) Other on-site clinical diagnoses

The on-site clinical diagnoses established at T=3 after seeing the scan and at T = 18 and T = 36 after imaging were not included in any endpoint defined in the statistical analysis plan or the clinical study protocol. Therefore, it was not required to code these diagnoses as either PD or non-PD. Results are presented in Section 14.2, Tables [14.2.2.4.1.2] (T=3), [14.2.3.4.3] (T = 18), and [14.2.4:5.1.2] (T = 36) of the European PDT304 CSR.

11.3.1.2 Analysis of primary efficacy endpoints

(a) Sensitivity, specificity, accuracy, PPV, and NPV for a) the on-site SPECT read and b) the independent SPECT BIE readers at T = 0 compared to the clinical diagnosis established by 2 independent MDS in consensus, based on the assessment of a video taken at T = 36.

All of these endpoints were determined and reported in the original European PDT304 CSR. However, in this report, only sensitivity and specificity are reported, because they are not sensitive to prevalence of the abnormality being detected, as are accuracy, PPV, and NPV. In addition, the order of reporting (BIE first, followed by the on-site results) is reversed from the European PDT304 CSR because the BIE results are believed to be less subject to bias. The analysis population for this endpoint is described in Section 11.1.

The results of the SPECT reads are shown in Section 11.3.1.5 (Table [25]) of the European PDT304 CSR. Table [26] (Section 11.3.1.5) of the European PDT304 CSR summarizes the binary results for the SPECT read.

BIE Results

Table 16 presents, for the Month-36 ITD population, the results of the baseline independent BIE SPECT reads versus the Month-36 SOT striatal assessment. Sensitivity for the detection of a SDD (i.e., loss of dopaminergic nigrostriatal neurons) ranged from 77.5% to 78.6% (mean across all 3 readers, 77.99%); specificity was 96.8% for all 3 readers (mean, 96.77%). These numbers match exactly the results reported in the European PDT304 CSR (with the exception of the mean values, which were not reported in the European PDT304 CSR). Results for the PP population were similar (Section 14.2, Table [14.2.9.2]).

Table 16 Baseline (T = 0) SPECT BIE Assessment by Reader Versus the Final (36-Month) SOT Diagnosis – M36 ITD Population

	36-Month SOT Diagnosis			
Baseline SPECT BIE Assessment	**Probable PD (SDD) n (%)**	**Possible PD (SDD) n (%)**	**Non-PD (No SDD) n (%)**	**Total n (%)**
Reader A				
Abnormal (SDD)	55 (54)	0 (0)	1 (1)	56 (55)
Normal (No SDD)	11 (11)	5 (5)	30 (29)	46 (45)
Total	66 (65)	5 (5)	31 (30)	102
Reader B				
Abnormal (SDD)	53 (54)	0 (0)	1 (1)	54 (55)
Normal (No SDD)	10 (10)	5 (5)	30 (30)	45 (45)
Total	63 (64)	5 (5)	31 (31)	99
Reader C				
Abnormal (SDD)	55 (54)	0 (0)	1 (1)	56 (55)
Normal (No SDD)	10 (10)	5 (5)	30 (30)	45 (45)
Total	65 (64)	5 (5)	31 (31)	101

Table 16 Baseline (T = 0) SPECT BIE Assessment by Reader Versus the Final (36-Month) SOT Diagnosis – M36 ITD Population

Analysis Summary	Statistic	Reader A: SDD[b] vs. No SDD	Reader B: SDD[b] vs. No SDD	Reader C: SDD[b] vs. No SDD	Mean (SD) across readers
Sensitivity	%	77.5	77.9	78.6	**77.99**
	(95% CI) [a]	(66.0, 86.5)	(66.2, 87.1)	(67.1, 87.5)	(0.555)
Specificity	%	96.8	96.8	96.8	**96.77**
	(95% CI) [a]	(83.3, 99.9)	(83.3, 99.9)	(83.3, 99.9)	(0.000)

n = number of subjects in each category; SDD = striatal dopaminergic deficit (loss of dopaminergic nigrostriatal neurons); PD = Parkinson's Disease; SOT = standard of truth; BIE = blinded image evaluation.
Percentage based on the number of subjects with both evaluations.
M36 ITD = Subjects who underwent SPECT imaging after receiving DaTSCAN™ and underwent the 36-month SOT assessment.
[a] CI = exact (95%; 2-sided).
[b] SDD = Probable or Possible PD for 36-month SOT diagnosis.
REF: Section 14.2, Table [14.2.9.1].

On-site SPECT Read

Table 17 presents, for the Month-36 ITD population, the results of the baseline on-site SPECT read versus the Month-36 SOT striatal assessment. Sensitivity was 80.3% (95% CI, 69.1% to 88.8%) and specificity for the absence of a SDD was 90.3% (95% CI, 74.2% to 98.0%). These results are similar to the BIE results (mean sensitivity and specificity 78% and 97%, respectively), and also match exactly the results reported in the European PDT304 CSR. Results for the PP population were similar (Section 14.2, Table [14.2.12.2).

Table 17 Baseline (T = 0) On-Site SPECT Read Versus the 36-Month SOT Diagnosis – M36 ITD Population

		36-Month SOT Diagnosis			
Baseline On-Site SPECT Read		**Probable PD (SDD) n (%)**	**Possible PD (SDD) n (%)**	**Non-PD (No SDD) n (%)**	**Total n (%)**
Abnormal (SDD)		56 (55)	1 (1)	3 (3)	60 (59)
Normal (No SDD)		10 (10)	4 (4)	28 (27)	42 (41)
Total		66 (65)	5 (5)	31 (30)	102
Analysis Summary	**Statistic**	**SDD[b] vs. No SDD**			
Sensitivity	% (95% CI) [a]	**80.3** (69.1, 88.8)			
Specificity	% (95% CI) [a]	**90.3** (74.2, 98.0)			

n = number of subjects in each category; SDD = striatal dopaminergic deficit (loss of dopaminergic nigrostriatal neurons); PD = Parkinson's Disease; SOT = standard of truth.
Percentage based on the number of subjects with both evaluations.
NOTE: Subjects classified as "Other" were tabulated as "Non-PD."
M36 ITD = Subjects who underwent SPECT imaging after receiving DaTSCAN™ and underwent the 36-month SOT assessment.
[a] CI = exact (95%; 2-sided).
[b] SDD = Probable or Possible PD for 36-month SOT diagnosis.
REF: Section 14.2, Table [14.2.12.1].

Accuracy, PPV, and NPV are discussed in the European PDT304 CSR. Accuracy was 83.3% (CI: 74.7% to 90.0%; Section 11.3.2.1, Table [42] of the European PDT304 CSR). PPV was 95.0% (Section 11.3.2.1, Table [43] of the European PDT304 CSR) and NPV was 66.7% (Section 11.3.2.1, Table [44] of the European PDT304 CSR).

11.3.1.3 Analysis of secondary efficacy endpoints

(a) Secondary endpoint A: Sensitivity, specificity, accuracy, PPV, and NPV for a) the on-site SPECT read and b) the independent SPECT BIE readers at T = 0 compared to the clinical diagnosis given by an on-site neurologist at T=3 (blinded to the results of the SPECT read).

Because the SOT diagnoses made at T = 18 and T = 36 by independent MDS are considered more robust than the on-site diagnoses made at T=3, this endpoint is not reported in this CSR. The results reported in the European PDT304 CSR are summarized in Table 18.

Table 18 Summary of Sensitivity and Specificity for On-Site and BIE Image Assessments and On-Site Clinical Diagnosis Using Clinical Diagnosis of an On-Site Neurologist as Reference Standard

Assessment	Sensitivity	Specificity
On-site SPECT read (T = 0)	82.3%	90.7%
BIE SPECT Read (T = 0)	80.0% to 80.6%	90.7% to 93.0%
On-Site Clinical Diagnosis (T = 0)	99.2%	70.0%

(b) Secondary endpoint B: Sensitivity, specificity, accuracy, PPV, and NPV for a) the on-site SPECT read and b) the independent SPECT BIE readers at T = 0 compared to the clinical diagnosis established by 2 independent MDS at T = 18 and T = 36.

The primary differences between this endpoint and the primary endpoint are: 1) use of the interim (T = 18) SOT and 2) reporting of the results by individual IIE reviewers, rather than using consensus assessments (no consensus resolution of inter-reader disagreement was performed at T = 18). Although the analysis of efficacy was conducted separately for each of the 2 IIE reviewers at T = 36, the results were not reported in the original European PDT304 CSR (because the consensus diagnoses were judged to be more reliable), and are accordingly not reported here. Therefore, only the results using the interim (T = 18) SOT are reported here. This endpoint was included because of the high dropout rate in the study (of the original 179 subjects dosed at T = 0, only 99 (55%) were still in the study at T = 36). The number of subjects evaluated at T = 18 was 128 (72% of the original 179 subjects).

This endpoint consisted of the comparison of 4 SPECT reads (3 BIE, 1 on-site) at T = 0 to the video-based decisions of the individual MDS at T = 18. Because there was no consensus resolution of inter-reader disagreement at T = 18, for each set of results only 1 of the independent video reader's assessments served as SOT. Sensitivity and specificity are shown in Table 19 and Table 20, respectively. The analysis population for this endpoint is described in Section 11.1.

Independent SPECT BIE Readers

The mean sensitivity across all 3 readers for the BIE read at T = 0 was 67.2% (using IIE reader 1's assessment as the interim SOT) and 70.5% (using IIE reader 2's assessment as the interim SOT) (Table 19). The mean specificity was 75.0% (IIE reader 1) and 82.2% (IIE reader 2) (Table 20). These results are very close to, but do not match exactly, the results as reported in the European PDT304 CSR. Slight differences in definition of the efficacy population likely account for the differences, which are not clinically significant. Data used to determine sensitivity and specificity are in Section 14.2, Table [14.2.5.1]. Results for the PP Population are similar; the analyses may be found in Section 14.2, Table [14.2.5.2]. For the other endpoints (accuracy, PPV, and NPV), see the statistical report (Section [16.1.9])of the European PDT304 CSR.

A direct comparison of these results with those using the final (36-month) SOT (Table 21) shows that mean sensitivity and specificity were both higher when based on the final (T = 36) SOT. Since the same DaTSCAN™ BIE image assessments were used at both time points,

these results indicate that the SOT changed in the direction of greater agreement with the DaTSCAN™ image assessments. This indicates that the visual assessment of DaTSCAN™ images made at T = 0 was about as reliable as expert diagnoses made 36 months later.

Table 19 Sensitivity of DaTSCAN™ SPECT Reads and On-site Clinical Diagnosis at T = 0 Compared to the Interim (T = 18) SOT

Video Reader	Read	N	N'	n	Sensitivity (%)	95% CI	
						Lower Limit	Upper Limit
Reader 1	On-site SPECT Read	128	100	71	71.0	61.1	89.3
	Independent SPECT BIE:						
	SPECT Reader A	128	100	67	67.0	56.9	76.1
	SPECT Reader B	125	97	65	67.0	56.7	76.2
	SPECT Reader C	127	99	67	67.7	57.5	76.7
	Mean across BIE readers				67.2		
Reader 2	On-site SPECT Read	125	95	70	73.7	63.6	82.2
	Independent SPECT BIE:						
	SPECT Reader A	125	95	67	70.5	60.3	79.4
	SPECT Reader B	122	92	64	69.6	59.1	78.7
	SPECT Reader C	124	94	67	71.3	61.0	80.1
	Mean across BIE readers				70.5		

N = Efficacy population for respective parameter.
N' = Number of subjects diagnosed with PD by T = 18 video assessment and non-missing values by respective read (SPECT or clinical diagnosis).
n = Number of subjects diagnosed with PD by T = 18 video assessment and respective read.
% = n/N' *100
REF: Section 14.2, Tables [14.2.1.1.a], [14.2.1.1.b], [14.2.3.1.a], [14.2.3.1.b]; and [14.2.5.1].

Table 20 Specificity of DaTSCAN™ SPECT Reads and On-site Clinical Diagnosis at T = 0 Compared to the Interim (T = 18) SOT

Video Reader	Read	N	N'	n	Specificity (%)	95% CI	
						Lower Limit	Upper Limit
Reader 1	On-site SPECT Read	128	28	21	75.0	55.1	89.3
	Independent SPECT BIE:						
	SPECT Reader A	128	28	21	75.0	55.1	89.3
	SPECT Reader B	125	28	21	75.0	55.1	89.3
	SPECT Reader C	127	28	21	75.0	55.1	89.3
	Mean across BIE readers				75.0		
Reader 2	On-site SPECT Read	125	30	24	80.0	61.4	92.3
	Independent SPECT BIE:						
	SPECT Reader A	125	30	25	83.3	65.3	94.4
	SPECT Reader B	122	30	24	80.0	61.4	92.3
	SPECT Reader C	124	30	25	83.3	65.3	94.4
	Mean across BIE readers				82.2		

N = Efficacy population for respective parameter.
N' = Number of subjects diagnosed as non-PD by T = 18 video assessment and non-missing values by respective read (SPECT or clinical diagnosis).
n = Number of subjects diagnosed as non-PD by T = 18 video assessment and respective read.
% = n/N' *100
REF: Section 14.2, Tables [14.2.1.1.a], [14.2.1.1.b], [14.2.3.1.a], [14.2.3.1.b]; and [14.2.5.1].

Table 21 Comparison of BIE Results Using Final (36-month) SOT vs. Interim (18-month) SOT

Standard of Truth	Mean Sensitivity	Mean Specificity
Final (36-month, consensus)	78.0%	96.8%
Interim (18-month, IIE Reader 1)	67.2%	75.0%
Interim (18-month, IIE Reader 2)	70.5%	82.2%

On-site SPECT Read

The sensitivity for the on-site SPECT read at T = 0 (Table 19) was 71.0% (IIE reader 1) and 73.7% (IIE reader 2); specificity (Table 20) was 75.0% and 80.0%, respectively. These results are very similar to the BIE results. Data used to determine sensitivity and specificity are in Section 14.2, Table [14.2.3.1.a] (reader 1) and Table [14.2.3.1.b] (reader 2). Results for the PP population are similar; the analyses may be found in Section 14.2, Table [14.2.3.2.a] (reader 1) and Table [14.2.3.2.b] (reader 2). A detailed tabulation of accuracy, NPV, and PPV can be found in the statistical report (Section [16.1.9])of the European PDT304 CSR.

(c) Secondary endpoint C: Sensitivity, specificity, accuracy, PPV, and NPV for the on-site clinical diagnosis at T = 0 compared to the clinical diagnosis established by 2 independent MDS at T = 18 and T = 36.

Although each of these parameters was determined and reported in the European PDT304 CSR, only sensitivity and specificity are reported here (because accuracy, PPV, and NPV depend on the prevalence of the abnormality being detected, whereas sensitivity and specificity do not). Analysis of the T = 18 on-site clinical diagnosis is also included here, although it was not reported in the European PDT304 CSR.

T = 0 On-Site Clinical Diagnosis

This T = 0 on-site clinical diagnosis was established at the centers during the T = 0 screening visit and before DaTSCAN™ SPECT imaging. It is considered representative of the ability of current clinical practice (in the absence of DaTSCAN™) to assess patients with symptoms and signs of movement disorders as having PD (as an indicator of a SDD) or not.

Sensitivity and specificity are shown for T = 36 in Table 22 and for T = 18 in Table 23 (for IIE reader 1) and in Table 24 (for IIE reader 2). The results vary by patient population. When deciding between Probable PD (indicating a SDD) and non-PD (indicating no SDD), the on-site physicians had higher sensitivity (90.5%) but lower specificity (80.0%) than the BIE readers (mean sensitivity and specificity of 78% and 97%, respectively). When subjects with "possible" PD (in whom the diagnosis was less certain) were included, sensitivity increased modestly while specificity decreased dramatically, or vice versa, depending on whether these subjects were classified as PD (SDD) or non-PD (no SDD). In all cases, the overall performance of the BIE readers was clinically significantly better than the on-site clinical diagnoses in detecting subjects with a SDD.

Sensitivity and specificity for the PP population were similar, and are in Section 14.2, Table [14.2.7.2] and Section 14.2, Table [14.2.1.2.a] (vs. reader 1) and Table [14.2.1.2.b] (vs. reader 2).

A detailed tabulation of accuracy, NPV, and PPV for T = 36 can be found in Table [42], Table [43], and Table [44] (Section 11.3.2.1) of the European PDT304 CSR. A detailed tabulation of accuracy, NPV, and PPV for T = 18 can be found in the statistical report (Section [16.1.9]) of the European PDT304 CSR.

Table 22 Baseline (T = 0) Pre-DaTSCAN™ On-Site Clinical Diagnosis Versus the Final (36-Month) SOT Assessment – M36 ITD Population

Baseline On-Site Pre-DaTSCAN™ Assessment	Final (36-month) SOT Assessment: Probable PD (SDD) n (%)	Possible PD (SDD) n (%)	Non-PD (no SDD) n (%)	Total n (%)
Probable PD (SDD)	38 (37)	2 (2)	4 (4)	44 (43)
Possible PD (SDD)	24 (24)	2 (2)	11 (11)	37 (36)
Non-PD (No SDD)	4 (4)	1 (1)	16 (16)	21 (21)
Total	66 (65)	5 (5)	31 (30)	102

Analysis Summary	Statistic	Probable PD (SDD) vs. Non-PD (no SDD)	Probable or Possible PD (SDD) vs. Non-PD (no SDD)	Probable PD (SDD) vs. Possible PD or Non-PD (no SDD)
Sensitivity	% (95% CI) [a]	90.5 (77.4, 97.3)	93.0 (84.3, 97.7)	57.6 (44.8, 69.7)
Specificity	% (95% CI) [a]	80.0 (56.3, 94.3)	51.6 (33.1, 69.8)	83.3 (67.2, 93.6)

n = number of subjects in each category; SDD = striatal dopaminergic deficit (i.e., loss of dopaminergic nigrostriatal neurons); PD = Parkinson's Disease; SOT = standard of truth.
Percentage based on the number of subjects with both evaluations.
NOTE: Subjects classified as "Benign PD" were tabulated as "Possible PD," and subjects classified as "Other" were tabulated as "Non-PD."
M18 ITD = Subjects who underwent SPECT imaging after receiving DaTSCAN™ and underwent the 36-month SOT assessment.
[a] CI = exact (95%; 2-sided).
REF: Section 14.2, Table [14.2.7.1].

Table 23 Baseline (T = 0) Pre-DaTSCAN™ On-Site Clinical Diagnosis Versus the Interim (18-Month) SOT Assessment - M18 ITD Population, Independent Video Evaluation: Reader 1

Baseline On-Site Pre-DaTSCAN™ Assessment	18-Month SOT Assessment: Reader 1 (N=128) Probable PD (SDD) n (%)	Possible PD (SDD) n (%)	Non-PD (no SDD) n (%)	Total n (%)
Probable PD (SDD)	45 (35)	2 (2)	6 (5)	53 (41)
Possible PD (SDD)	33 (26)	5 (4)	13 (10)	51 (40)
Non-PD (no SDD)	11 (9)	4 (3)	9 (7)	24 (19)
Total	89 (70)	11 (9)	28 (22)	128

Analysis Summary	Statistic	Probable PD vs. Non-PD	Probable or Possible PD vs. Non-PD	Probable PD vs. Possible PD or Non-PD
Sensitivity	% (95% CI) [a]	80.4 (67.6, 89.8)	85.0 (76.5, 91.4)	50.6 (39.8, 61.3)
Specificity	% (95% CI) [a]	60.0 (32.3, 83.7)	32.1 (15.9, 52.4)	79.5 (63.5, 90.7)

n = number of subjects in each category; SDD = striatal dopaminergic deficit (i.e., loss of dopaminergic nigrostriatal neurons); PD = Parkinson's Disease; SOT = standard of truth.
Percentage based on the number of subjects with both evaluations.
NOTE: Subjects classified as "Benign PD" were tabulated as "Possible PD," and subjects classified as "Other" were tabulated as "Non-PD."
M18 ITD = Subjects who underwent SPECT imaging after receiving DaTSCAN™ and underwent the 18-month SOT assessment.
[a] CI = exact (95%; 2-sided).
REF: Section 14.2, Table [14.2.1.1.a].

Table 24 Baseline (T = 0) Pre-DaTSCAN™ On-Site Clinical Diagnosis Versus the Interim (18-Month) SOT Assessment - M18 ITD Population, Independent Video Evaluation: Reader 2

Baseline On-Site Pre-DaTSCAN™ Assessment	18-Month SOT Assessment: Reader 2 (N=128) Probable PD (SDD) n (%)	Possible PD (SDD) n (%)	Non-PD (no SDD) n (%)	Total n (%)
Probable PD (SDD)	42 (34)	5 (4)	6 (5)	53 (42)
Possible PD (SDD)	23 (18)	15 (12)	10 (8)	48 (38)
Non-PD (no SDD)	4 (3)	6 (5)	14 (11)	24 (19)
Total	69 (55)	26 (21)	30 (24)	125

Analysis Summary	Statistic	Probable PD (SDD) vs. Non-PD (no SDD)	Probable or Possible PD (SDD) vs. Non-PD (no SDD)	Probable PD (SDD) vs. Possible PD or Non-PD (no SDD)
Sensitivity	% (95% CI) [a]	91.3 (79.2, 97.6)	89.5 (81.5, 94.8)	60.9 (48.4, 72.4)
Specificity	% (95% CI) [a]	70.0 (45.7, 88.1)	46.7 (28.3, 65.7)	80.4 (67.6, 89.8)

n = number of subjects in each category; SDD = striatal dopaminergic deficit (i.e., loss of dopaminergic nigrostriatal neurons); PD = Parkinson's Disease; SOT = standard of truth.
Percentage based on the number of subjects with both evaluations.
NOTE: Subjects classified as "Benign PD" were tabulated as "Possible PD," and subjects classified as "Other" were tabulated as "Non-PD."
M18 ITD = Subjects who underwent SPECT imaging after receiving DaTSCAN™ and underwent the 18-month SOT assessment.
[a] CI = exact (95%; 2-sided).
REF: Section 14.2, Table [14.2.1.1.b].

T = 18 On-Site Clinical Diagnosis

This endpoint served to test the efficacy of the on-site clinical diagnosis when compared to the SOT. The T = 18 on-site clinical diagnosis was analyzed in a manner similar to the results of the DaTSCAN™ SPECT image analysis. The T = 18 on-site clinical diagnosis was established at the centers during before T = 18 DaTSCAN™ SPECT imaging. The clinical diagnosis was compared to the diagnosis of the independent MDS from a video assessment together with relevant clinical information at T = 18 and T = 36. The sensitivity and specificity were calculated. For T = 36 the consensus diagnosis of the 2 independent video assessors served as the SOT. For T = 18 the analysis was performed for each of these 2 independent MDS separately, since a consensus result was not available.

Sensitivity and specificity of the on-site clinical diagnosis at T = 18 compared to the final (T = 36) SOT are shown in Table 25. Sensitivity and specificity of the on-site clinical diagnosis at T = 18 vs. the interim (T = 18) SOT are shown in Table 26 (vs. reader 1) and Table 27 (vs. reader 2). For both comparisons, the sensitivity of the on-site clinical diagnosis was higher than that of the SPECT reads. At T = 18, the sensitivity was 91.5% (Table 25). However, the specificity was only 58.1% (Table 25). Thus, although the T = 18 on-site clinical diagnosis was more sensitive than SPECT imaging, the on-site investigators tended to "over-diagnose" a subject as having PD when compared to DaTSCAN™ SPECT. The results for the T = 18 on-site clinical diagnosis vs. the interim (T = 18) SOT were similar (Table 26 and Table 27, for readers 1 and 2, respectively).

Table 25 Month-18 Pre-Dose On-Site Clinical Diagnosis Versus the 36-Month SOT Diagnosis – M36 ITD Population

Month-18 On-Site Pre-DaTSCAN™ Assessment	36-Month SOT Diagnosis			
	Probable PD n (%)	Possible PD n (%)	Non-PD n (%)	Total n (%)
Probable PD	41 (40)	2 (2)	3 (3)	46 (45)
Possible PD	20 (20)	2 (2)	10 (10)	32 (31)
Non-PD	5 (5)	1 (1)	18 (18)	24 (24)
Total	66 (65)	5 (5)	31 (30)	102

Analysis Summary	Statistic	Probable PD vs. Non-PD	Probable or Possible PD vs. Non-PD	Probable PD vs. Possible PD or Non-PD
Sensitivity	%	89.1	91.5	62.1
	(95% CI) [a]	(76.4, 96.4)	(82.5, 96.8)	(49.3, 73.8)
Specificity	%	85.7	58.1	86.1
	(95% CI) [a]	(63.7, 97.0)	(39.1, 75.5)	(70.5, 95.3)

n = number of subjects in each category; PD = Parkinson's Disease; SOT = standard of truth.
Percentage based on the number of subjects with both evaluations.
NOTE: Subjects classified as "Benign PD" were tabulated as "Possible PD," and subjects classified as "Other" were tabulated as "Non-PD."
M36 ITD = Subjects who underwent SPECT imaging after receiving DaTSCAN™ and underwent the 36-month SOT assessment.
[a] CI = exact (95%; 2-sided).
REF: Section 14.2, Table [14.2.8.1].

Table 26 Month-18 Pre-Dose On-Site Clinical Diagnosis Versus the 18-Month SOT Diagnosis - M18 ITD Population, Independent Video Evaluation: Reader 1

Month-18 On-Site Pre-DaTSCAN™ Assessment	18-Month SOT Diagnosis: Reader 1 (N=128)			
	Probable PD n (%)	Possible PD n (%)	Non-PD n (%)	Total n (%)
Probable PD	47 (37)	3 (2)	8 (6)	58 (45)
Possible PD	30 (23)	4 (3)	7 (5)	41 (32)
Non-PD	12 (9)	4 (3)	13 (10)	29 (23)
Total	89 (70)	11 (9)	28 (22)	128

Analysis Summary	Statistic	Probable PD vs. Non-PD	Probable or Possible PD vs. Non-PD	Probable PD vs. Possible PD or Non-PD
Sensitivity	%	79.7	84.0	52.8
	(95% CI) [a]	(67.2, 89.0)	(75.3, 90.6)	(41.9, 63.5)
Specificity	%	61.9	46.4	71.8
	(95% CI) [a]	(38.4, 81.9)	(27.5, 66.1)	(55.1, 85.0)

n = number of subjects in each category; PD = Parkinson's Disease; SOT = standard of truth.
Percentage based on the number of subjects with both evaluations.
NOTE: Subjects classified as "Benign PD" or "Possible PSP" were tabulated as "Possible PD," and subjects classified as "Other" were tabulated as "Non-PD."
M18 ITD = Subjects who underwent SPECT imaging after receiving DaTSCAN™ and underwent the 18-month SOT assessment.
[a] CI = exact (95%; 2-sided).
REF: Section 14.2, Table [14.2.2.1].

Table 27 Month-18 Pre-Dose On-Site Clinical Diagnosis Versus the 18-Month SOT Diagnosis - M18 ITD Population, Independent Video Evaluation: Reader 2

Month-18 On-Site Pre-DaTSCAN™ Assessment	18-Month SOT Diagnosis: Reader 2 (N=125)			
	Probable PD n (%)	Possible PD n (%)	Non-PD n (%)	Total n (%)
Probable PD	47 (38)	5 (4)	5 (4)	57 (46)
Possible PD	19 (15)	13 (10)	7 (6)	39 (31)
Non-PD	3 (2)	8 (6)	18 (14)	29 (23)
Total	69 (55)	26 (21)	30 (24)	125

Analysis Summary	Statistic	Probable PD vs. Non-PD	Probable or Possible PD vs. Non-PD	Probable PD vs. Possible PD or Non-PD
Sensitivity	%	94.0	88.4	68.1
	(95% CI) [a]	(83.5, 98.7)	(80.2, 94.1)	(55.8, 78.8)
Specificity	%	78.3	60.0	82.1
	(95% CI) [a]	(56.3, 92.5)	(40.6, 77.3)	(69.6, 91.1)

n = number of subjects in each category; PD = Parkinson's Disease; SOT = standard of truth.
Percentage based on the number of subjects with both evaluations.
NOTE: Subjects classified as "Benign PD" or "Possible PSP" were tabulated as "Possible PD," and subjects classified as "Other" were tabulated as "Non-PD."
M18 ITD = Subjects who underwent SPECT imaging after receiving DaTSCAN™ and underwent the 18-month SOT assessment.
[a] CI = exact (95%; 2-sided).
REF: Section 14.2, Table [14.2.2.1].

Sensitivity and specificity in the PP population for the on-site clinical diagnosis at T = 18 compared to final (36-month) SOT were similar to the ITD population analysis, and can be found in Section 14.2, Table [14.2.8.2]. Sensitivity and specificity in the PP population for the on-site clinical diagnosis at T = 18 compared to the interim (18 month) SOT were likewise similar to the ITD population analysis, and can be found in Section 14.2, Table [14.2.2.2].

(d) Secondary endpoint D: Exploratory analyses of the groups of probable PD, possible PD, and non-PD as determined by the IIE video assessment at T = 36.

Sensitivity, specificity, accuracy, NPV, and PPV for the independent SPECT BIE readers at T = 0 compared to the final (36-month) SOT were calculated. Subjects diagnosed according to the final SOT as "possible Parkinsonism" were excluded from the analysis.

This was the case for a total of 5 subjects. Therefore, the efficacy population for this analysis consists of only 97 subjects for the on-site SPECT image diagnosis for reader A, 94 subjects for reader B, and 96 subjects for reader C (see Section 11.1). As the 5 subjects excluded from the analysis were classified as having PD, there was no difference in specificity compared to that obtained for all subjects. Results for sensitivity are presented in Section [11.3.2.5] of the European PDT304 CSR. Results for accuracy, PPV, and NPV are presented in Section [14.2.7] of the European PDT304 CSR. Due to the small difference between the

2 groups of subjects analyzed, there was only a slight difference when compared to the results of the primary endpoint.

For all 5 possible PD subjects, all 3 blinded SPECT readers classified the DaTSCAN™ images as normal instead of abnormal. Sensitivity and consequently accuracy were higher compared to the analysis that included all subjects. The on-site SPECT read classified 4 out of the 5 respective images incorrectly. This lends credibility to the assumption that subjects with possible PD are difficult to diagnose on the basis of the presently accepted clinical criteria. Nevertheless, a high inter-reader agreement can be seen: the SPECT image classification was identical between all 3 readers.

A complete description of the results of this exploratory analysis may be found in Section [11.3.2.5] of the European PDT304 CSR.

(e) Secondary endpoint E: Confidence levels of the clinical diagnosis of idiopathic PD.

The clinicians' COD generally increased after becoming aware of DaTSCAN™ SPECT image results.

Results for the clinician's COD can be found in the statistical report (Section [16.1.9])of the European PDT304 CSR and in Section 14.2 (Tables [14.2.1.3.2], [14.2.2.3.2], [14.2.2.4.2], [14.2.3.3.2], [14.2.3.4.4], [14.2.4.3.3] and [14.2.4.5.2]) and Section [16.2.4] of the European PDT304 CSR.

(f) Secondary endpoint F: Sensitivity, specificity, accuracy, NPV, and PPV for the independent SPECT readers at T = 0 compared to the on-site clinical diagnosis at T = 18 and T = 36.

This analysis was performed because it was felt that the on-site clinical diagnosis might reflect the true disease status of a subject more accurately than the IIE video assessment. Since the investigator followed the entire clinical course of the subject face-to-face for a considerable length of time, it was considered to be the most accurate ante-mortem diagnosis possible. Two limitations of this analysis are that this diagnosis is not independent and the on-site physician had knowledge of the T = 0 scan results. However, the diagnosis during the T = 18 screening visit was independent of T = 18 SPECT imaging and the diagnosis during the T = 36 screening visit was independent of T = 36 SPECT imaging.

The results of sensitivity, specificity, accuracy, PPV, and NPV are shown in Section 14.2, Table [14.2.7.2.3] (T = 18) and Table [14.2.7.2.8] (T = 36) of the European PDT304 CSR.

For the comparison of the T = 0 SPECT BIE results to the on-site clinical diagnosis at T = 18, the SPECT results exceeded the results of endpoint B for each of the 3 SPECT BIE readers: the sensitivity ranged from 83.0% to 83.9%. The specificity is even higher; only 1 out of 40 non-PD subjects had been incorrectly classified as having PD, resulting in a specificity of 97.5%. All SPECT readers rated all subjects identically.

For the comparison of the T = 0 SPECT BIE results to the on-site clinical diagnosis at T = 36, the SPECT results also exceeded the results of the primary endpoint: sensitivity ranged from 82.4% to 83.6% (primary endpoint 77.5% to 78.6%): The specificity was 100%; all negative subjects were correctly diagnosed as normal by all 3 readers (primary endpoint 96.8%, only 1 subject was classified incorrectly).

For the comparison of T = 0 SPECT BIE results to the clinical diagnosis at T = 18, the results were far better if the on-site clinical diagnosis was used as SOT instead of the IIE video assessment. For the comparison of T = 0 SPECT BIE results to the clinical diagnosis at T = 36, the results were still better if the on-site clinical diagnosis was used as SOT instead of the IIE video assessment. However, the difference between the time points was far less distinctive.

(g) Secondary endpoint G: Analysis of the stability of DaTSCAN™ SPECT findings (institutional visual read and independent SPECT read) over time: sensitivity, specificity, accuracy, PPV, and NPV for both the institutional SPECT and the independent SPECT BIE readers at T = 18 and T = 36 compared to the consensus diagnosis established by 2 independent MDS at T = 36.

Only the analyses of sensitivity and specificity are reported here, because they are the only metrics which do not depend upon the prevalence of the abnormality being tested. Analyses of accuracy, PPV, and NPV are reported in the European PDT304 CSR.

Since the major purpose of this study was to assess the efficacy of DaTSCAN™ images at T = 0, the independent SPECT BIE of the T = 0 images (discussed above) is the most important endpoint. SPECT reads were also performed at T = 18 and T = 36 to assess stability of the T = 0 findings. The results remained stable when compared to the T = 0 read. The following sections present the results for the ITD population. In all analyses the results using the PP population were similar; the locations of the comparative results for the PP population are also indicated.

Results are reported here only for the BIE and on-site image assessments using the final (36-month) SOT.

BIE Results

- Results for the Month-18 SPECT BIE assessment, by reader, versus the final (T = 36) SOT diagnosis are shown in Table 28 (results for the PP population are in Section 14.2, Table [14.2.10.2])

- Results for the Month-36 SPECT BIE assessment, by reader, versus the final (T = 36) SOT diagnosis are in Table 29 (results for the PP population are in Section 14.2, Table [14.2.11.2])

The mean results from the BIE SPECT assessments at T = 18 (Table 28) and T = 36 (Table 29) with the results from T = 0 (Table 16) are summarized in Table 30. These show excellent stability of the BIE SPECT findings over time.

Table 28 Month-18 SPECT BIE Assessment by Reader Versus the 36-Month SOT Diagnosis – M36 ITD Population

Month-18 SPECT BIE Assessment	36-Month SOT Diagnosis: Probable PD n (%)	Possible PD n (%)	Non-PD n (%)	Total n (%)
Reader A				
Abnormal (PD)	55 (54)	0 (0)	1 (1)	56 (55)
Normal (Non-PD)	11 (11)	5 (5)	29 (29)	45 (45)
Total	66 (65)	5 (5)	30 (30)	101
Reader B				
Abnormal (PD)	54 (53)	1 (1)	2 (2)	57 (56)
Normal (Non-PD)	12 (12)	4 (4)	29 (28)	45 (44)
Total	66 (65)	5 (5)	31 (30)	102
Reader C				
Abnormal (PD)	57 (56)	1 (1)	1 (1)	59 (58)
Normal (Non-PD)	9 (9)	4 (4)	30 (29)	43 (42)
Total	66 (65)	5 (5)	31 (30)	102

Analysis Summary	Statistic	Reader A: PD[b] vs. Non-PD	Reader B: PD[b] vs. Non-PD	Reader C: PD[b] vs. Non-PD	Mean (SD) across readers
Sensitivity	% (95% CI) [a]	77.5 (66.0, 86.5)	77.5 (66.0, 86.5)	81.7 (70.7, 89.9)	**78.87** (2.440)
Specificity	% (95% CI) [a]	96.7 (82.8, 99.9)	93.5 (78.6, 99.2)	96.8 (83.3, 99.9)	**95.66** (1.832)

n = number of subjects in each category; PD = Parkinson's Disease; SOT = standard of truth; BIE = blinded image evaluation.
Percentage based on the number of subjects with both evaluations.
M36 ITD = Subjects who underwent SPECT imaging after receiving DaTSCAN™ and underwent the 36-month SOT assessment.
[a] CI = exact (95%; 2-sided).
[b] PD = Probable or Possible PD for 36-month SOT diagnosis.
REF: Section 14.2, Table [14.2.10.1].

Table 29 Month-36 SPECT BIE Assessment by Reader Versus the 36-Month SOT Diagnosis – M36 ITD Population

Month-36 SPECT BIE Assessment	36-Month SOT Diagnosis: Probable PD n (%)	Possible PD n (%)	Non-PD n (%)	Total n (%)
Reader A				
Abnormal (PD)	51 (52)	0 (0)	1 (1)	52 (53)
Normal (Non-PD)	12 (12)	5 (5)	29 (30)	46 (47)
Total	63 (64)	5 (5)	30 (31)	98
Reader B				
Abnormal (PD)	49 (52)	1 (1)	1 (1)	51 (54)
Normal (Non-PD)	11 (12)	4 (4)	29 (31)	44 (46)
Total	60 (63)	5 (5)	30 (32)	95
Reader C				
Abnormal (PD)	52 (53)	1 (1)	1 (1)	54 (55)
Normal (Non-PD)	11 (11)	4 (4)	29 (30)	44 (45)
Total	63 (64)	5 (5)	30 (31)	98

Analysis Summary	Statistic	Reader A: PD[b] vs. Non-PD	Reader B: PD[b] vs. Non-PD	Reader C: PD[b] vs. Non-PD	Mean (SD) across readers
Sensitivity	%	75.0	76.9	77.9	76.62
	(95% CI) [a]	(63.0, 84.7)	(64.8, 86.5)	(66.2, 87.1)	(1.494)
Specificity	%	96.7	96.7	96.7	96.67
	(95% CI) [a]	(82.8, 99.9)	(82.8, 99.9)	(82.8, 99.9)	(0.000)

n = number of subjects in each category; PD = Parkinson's Disease; SOT = standard of truth; BIE = blinded image evaluation.
Percentage based on the number of subjects with both evaluations.
M36 ITD = Subjects who underwent SPECT imaging after receiving DaTSCAN™ and underwent the 36-month SOT assessment.
[a] CI = exact (95%; 2-sided).
[b] PD = Probable or Possible PD for 36-month SOT diagnosis.
REF: Section 14.2, Table [14.2.11.1].

Table 30 Comparison of Sensitivity and Specificity of BIE SPECT Visual Assessments at T = 0, T = 18, and T = 36 (Using Final [36-month] SOT)

Analysis Summary	Statistic	Time of BIE Assessment: T = 0	T = 18	T = 36
Sensitivity	%	77.99	78.87	76.62
	(95% CI) [a]	(0.555)	(2.440)	(1.494)
Specificity	%	96.77	95.66	96.67
	(95% CI) [a]	(0.000)	(1.832)	(0.000)

[a] CI = exact (95%; 2-sided).
REF: Table 16, Table 28, and Table 29.

On-Site Image Assessments

- Month-18 on-site SPECT read versus the 36-month SOT diagnosis—Table 31 (PP Population—Section 14.2, Table [14.2.13.2])
- Month-36 on-site SPECT BIE read versus the 36-month SOT diagnosis—Table 32 (PP Population—Section 14.2, Table [14.2.14.2])

The mean results from the on-site SPECT assessments at T = 18 (Table 31) and T = 36 (Table 32) with the results from T = 0 (Table 17 above) are summarized in Table 33. These show excellent stability of the BIE SPECT findings over time.

Table 31 Month-18 On-Site SPECT Read Versus the 36-Month SOT Diagnosis – M36 ITD Population

Month-18 On-Site SPECT Read	36-Month SOT Diagnosis			Total
	Probable PD n (%)	Possible PD n (%)	Non-PD n (%)	n (%)
Abnormal (PD)	56 (55)	1 (1)	3 (3)	60 (59)
Normal (Non-PD)	9 (9)	4 (4)	28 (28)	41 (41)
Total	65 (64)	5 (5)	31 (31)	101

Analysis Summary	Statistic	PD[b] vs. Non-PD
Sensitivity	% (95% CI) [a]	**81.4** (70.3, 89.7)
Specificity	% (95% CI) [a]	**90.3** (74.2, 98.0)

n = number of subjects in each category; PD = Parkinson's Disease; SOT = standard of truth.
Percentage based on the number of subjects with both evaluations.
NOTE: Subjects classified as "Other" were tabulated as "Non-PD."
M36 ITD = Subjects who underwent SPECT imaging after receiving DaTSCAN™ and underwent the 36-month SOT assessment.
[a] CI = exact (95%; 2-sided).
[b] PD = Probable or Possible PD for 36-month SOT diagnosis.
REF: Section 14.2, Table [14.2.13.1].

Table 32 Month-36 On-Site SPECT Read Versus the 36-Month SOT Diagnosis – M36 ITD Population

Month-36 On-Site SPECT Read		36-Month SOT Diagnosis: Probable PD n (%)	Possible PD n (%)	Non-PD n (%)	Total n (%)
Abnormal (PD)		55 (57)	2 (2)	4 (4)	61 (63)
Normal (Non-PD)		8 (8)	3 (3)	25 (26)	36 (37)
Total		63 (65)	5 (5)	29 (30)	97
Analysis Summary	**Statistic**	**PD[b] vs. Non-PD**			
Sensitivity	% (95% CI) [a]	**83.8** (72.9, 91.6)			
Specificity	% (95% CI) [a]	**86.2** (68.3, 96.1)			

n = number of subjects in each category; PD = Parkinson's Disease; SOT = standard of truth.
Percentage based on the number of subjects with both evaluations.
NOTE: Subjects classified as "Other" were tabulated as "Non-PD."
M36 ITD = Subjects who underwent SPECT imaging after receiving DaTSCAN™ and underwent the 36-month SOT assessment.
[a] CI = exact (95%; 2-sided).
[b] PD = Probable or Possible PD for 36-month SOT diagnosis.
REF: Section 14.2, Table [14.2.14.1].

Table 33 Comparison of Sensitivity and Specificity of On-Site SPECT Visual Assessments at T = 0, T = 18, and T = 36 (Using Final (36-month) SOT)

		Time of BIE Assessment		
Analysis Summary	**Statistic**	**T= 0**	**T = 18**	**T = 36**
Sensitivity	% (95% CI) [a]	**80.3** (69.1, 88.8)	**81.4** (70.3, 89.7)	**83.8** (72.9, 91.6)
Specificity	% (95% CI) [a]	**90.3** (74.2, 98.0)	**90.3** (74.2, 98.0)	**86.2** (68.3, 96.1)

[a] CI = exact (95%; 2-sided).
REF: Table 17, Table 31, and Table 32.

(h) Secondary endpoint H: Inter-reader agreement between DaTSCAN™ SPECT readers; inter-reader agreement between independent video readers.

Inter-reader agreement between DaTSCAN™ SPECT readers at T = 0

The population consisted of 102 subjects in the ITD population who underwent SPECT imaging at T = 0 after receiving DaTSCAN™ and underwent the 36-month SOT assessment. For all pairwise comparisons involving reader B, 3 subjects were missing. When reader C was involved, 1 subject was missing (see Section 11.1). The agreement of the 3 independent SPECT readers as to whether the image was normal or abnormal was extremely high. The agreement rate was measured by κ coefficients. Pairwise κ coefficients were calculated for all pairs of the 3 independent BIE readers and the on-site SPECT read. The results of the pairwise κ coefficients with a 2-sided 95% CI are shown in Table 34. Inter-reader agreement results for the PP population SPECT reads at T = 0 are similar and are presented in Section 14.2, Table [14.2.15.2].

Table 34 Kappa Coefficients for the SPECT Read at T = 0 (Month-36 Intent-to-Diagnose Population)

SPECT Reader	N	n	Cohen's Kappa	95% CI	
				Lower	Upper
A vs. B	99	98	0.98	0.94	1.02
A vs. C	101	100	0.98	0.94	1.02
B vs. C	98	98	1.00	1.00	1.00
A vs. On-site	102	98	0.92	0.84	1.00
B vs. On-site	99	96	0.94	0.87	1.01
C vs. On-site	101	98	0.94	0.87	1.01
A, B, and C*	98	97	0.99	0.87	1.10

N = Number of images with non-missing value for DaTSCAN™ SPECT visual assessment for the 2 respective readers; for the generalized κ: number of images with non-missing values for all 3 readers; n = number of images with agreement

* Multiple κ coefficient for all 3 independent SPECT readers.

REF: Section 14.2, Table [14.2.15.1].

The pairwise κ coefficients calculated between the 3 pairs of independent BIE readers were almost perfect. The κ coefficients obtained for the on-site read and each of the independent readers were only slightly lower.

Additionally, a κ coefficient that combines all 3 independent BIE readers was calculated. The combined κ value was 0.99 for the 3 independent SPECT readers reflecting the extremely high agreement between the independent readers.

Inter-reader Agreement between DaTSCAN™ SPECT Readers at T = 18

The population consisted of 102 subjects in the ITD population who underwent SPECT imaging at T = 18 after receiving DaTSCAN™ and underwent the 36-month SOT assessment. For all pairwise comparisons involving reader B, 3 subjects were missing. When reader C was involved, 1 subject was missing (see Section 11.1). The agreement of the 3 independent SPECT readers as to whether the image was normal or abnormal was extremely high. The

agreement rate was measured by κ coefficients. Pairwise κ coefficients were calculated for all pairs of the 3 independent BIE readers and the on-site SPECT read. The results of the pairwise κ coefficients with a 2-sided 95% CI are shown in Table 35. Inter-reader agreement results for the PP population SPECT reads at T = 18 are similar and are presented in Section 14.2, Table [14.2.16.2].

Table 35 Kappa Coefficients for the SPECT Read at T = 18 (Month-36 Intent-to-Diagnose Population)

SPECT Reader	N	n	Cohen's Kappa (κ)	95% CI	
				Lower	Upper
A vs. B	101	98	0.94	0.87	1.01
A vs. C	101	98	0.94	0.87	1.01
B vs. C	102	98	0.92	0.84	1.00
A vs. On-site	100	95	0.90	0.81	0.98
B vs. On-site	101	95	0.88	0.78	0.97
C vs. On-site	101	97	0.92	0.84	1.00
A, B, and C*	101	96	0.96	0.93	1.05

N = Number of images with non-missing value for DaTSCAN™ SPECT visual assessment for the 2 respective readers; for the generalized κ: number of images with non-missing values for all 3 readers; n = number of images with agreement

* Multiple κ coefficient for all 3 independent SPECT readers.

REF: Section 14.2, Table [14.2.16.1].

The pairwise κ coefficients between the 3 pairs of independent BIE readers reached values between 0.92 and 0.94. The κ coefficients obtained for the on-site read and each of the independent readers were only slightly lower.

The combined κ coefficient for all 3 independent BIE readers was 0.96 reflecting the extremely high agreement between the independent readers.

Inter-reader Agreement between DaTSCAN™ SPECT Readers at T = 36

The population consisted of 102 subjects in the ITD population who underwent SPECT imaging at T = 36 after receiving DaTSCAN™ and underwent the 36-month SOT assessment. For all pairwise comparisons involving reader B, 3 subjects were missing. When reader C was involved, 1 subject was missing (see Section 11.1). The agreement of the 3 independent SPECT readers as to whether the image was normal or abnormal was extremely high. The agreement rate was measured by κ coefficients. Pairwise κ coefficients were calculated for all pairs of the 3 independent BIE readers and the on-site SPECT read. The results of the pairwise κ coefficients with a 2-sided 95% CI are shown in Table 36. Inter-reader agreement results for the PP population SPECT reads at T = 36 are similar and are presented in Section 14.2, Table [14.2.17.2].

Table 36 Kappa Coefficients for the SPECT Read at T = 36 (Month-36 Intent-to-Diagnose Population)

SPECT Reader	N	n	Cohen's Kappa (κ)	95% CI	
				Lower	Upper
A vs. B	94	92	0.96	0.90	1.02
A vs. C	97	95	0.96	0.90	1.02
B vs. C	95	95	1.00	1.00	1.00
A vs. On-site	95	87	0.83	0.72	0.94
B vs. On-site	92	86	0.87	0.77	0.97
C vs. On-site	95	89	0.87	0.87	0.97
A, B, and C*	94	92	0.97	0.85	1.09

N = Number of images with non-missing value for DaTSCAN™ SPECT visual assessment for the 2 respective readers; for the generalized κ: number of images with non-missing values for all 3 readers; n = number of images with agreement

* Multiple κcoefficient for all 3 independent SPECT readers.

REF: Section 14.2, Table [14.2.17.1].

The pairwise κ coefficients between the 3 pairs of independent BIE readers reached values between 0.96 and 1.00. The κ coefficients obtained for the on-site read and each of the independent readers were only slightly lower.

The combined κ coefficient for all 3 independent BIE readers was 0.97 reflecting the extremely high agreement between the independent readers.

Inter-reader Agreement between the Video Readers at T = 18 and T = 36

For both T = 18 and T = 36, the 2 MDS established all diagnoses individually. For T = 36, a consensus read was performed after the individual reading sessions. This consensus diagnosis served as the SOT. For the 2 individual reads at both time points a κ coefficient was calculated.

At T = 18, 125 videos were assessed by the first MDS, but only 122 videos by the second. Out of these 122 subjects, 23 (18.8%) were diagnosed differently. The κ coefficient was therefore only 0.37 with a CI between 0.17 and 0.58 (Section 16.1.9, Table [16.1.9.4] of the European PDT304 CSR).

At T = 36, 99 videos were read by the 2 readers. Thirteen (13.1%) of the subjects were rated differently by the 2 readers regarding PD or non-PD. The κ coefficient was 0.68 with a CI between 0.53 and 0.83 (Section 16.1.9, Table [16.1.9.4] of the European PDT304 CSR).

Compared to the SPECT reads, the agreement rate for the video-based expert clinical diagnosis was lower for both time points.

11.3.2 Descriptive Efficacy Analysis

Description of False Negative and False Positive Cases

FN results were defined as cases in which the 2 independent MDS (i.e., T = 36 consensus diagnosis as the SOT readers) determined the subject to have either possible or probable PD, whereas the DaTSCAN™ SPECT image at T = 0 was classified as being normal by all 3 independent BIE readers. Refer to Section [11.3.3.1] of the European PDT304 CSR for a discussion of the FN cases.

There was only 1 FP case, i.e., the SOT diagnosis was non-PD and the scan was judged as being abnormal by all 3 independent BIE readers. Refer to Section [11.3.3.1] of the European PDT304 CSR for a discussion of this case.

11.4 Efficacy Conclusions

- Based on blinded independent reads (using 3 readers), the mean sensitivity of visual assessment of DaTSCAN™ SPECT images for detecting or excluding a SDD, using the final (36-month) SOT, ranged from 77.99%, and the specificity was 96.8%. In contrast, on-site clinicians at baseline (T = 0) showed a definite tendency to over-diagnose a SDD (as indicated by a diagnosis of PD): although the sensitivity was high (93.0%), the specificity was extremely low (51.6%). Although the sensitivity of DaTSCAN™ imaging was lower than on-site diagnosis, the greater specificity of DaTSCAN™ images makes DaTSCAN™ overall a better test to detect or exclude a SDD.

- The sensitivity and specificity of the T = 0 SPECT images using the 36-month (final) SOT were both higher than when the T = 18 (interim) SOT was used. This convergence between DaTSCAN™ SPECT findings at baseline and the 36-month truth standard diagnosis supports the conclusion that subjects with SDD (e.g., in early PD) can be accurately detected by DaTSCAN™ imaging.

- The inter-reader agreement between the 3 blinded readers was extremely high (κ from 0.96 to 1.00). In contrast, κ values for the 2 video readers at both T = 18 (κ = 0.37) and T = 36 (κ = 0.68) were both lower, suggesting that DaTSCAN™ images may assist physicians in making more consistent assessments of patients with symptoms and signs of movement disorders.

- Comparison of the SPECT reads at T = 18 and T = 36 to the SPECT read at T = 0 revealed no clinically significant differences. The readers' assessments were very consistent over time, confirming that DaTSCAN™ can detect or exclude a SDD at a very early stage of symptoms.

12 SAFETY EVALUATION

The safety analysis that was performed for this CSR addresses only AEs, SAEs, and deaths. All other safety parameters that were collected during the study (physical examination, vital signs, clinical laboratory, including serum biochemistry, hematology, urinalysis, and urine microscopy/culture, and ECG) were analyzed and the results presented in the European PDT304 CSR. Results for these parameters are summarized briefly in this report.

AEs were recorded from the time of the first DaTSCAN™ administration until the 36-month telephone follow-up. Symptoms reported during the T = 18 and T = 36 screening visits had to be included in the overall AE counts as they occurred after the first DaTSCAN™ administration at T = 0.

12.1 Adverse Events

AEs were recorded during the entire course of the study. Depending on the visit type, AEs were not only recorded when occurring during the subject's visit at the study center, but also when reported via telephone (T = 0, T = 18, T = 36 telephone follow-up), and retrospectively when reported by the subject during the T = 18 and T = 36 screening visits. Thus, all AEs occurring between the visits at the investigational site over the entire course of the study were recorded. For the safety analysis, all AEs reported were equally listed and tabulated.

12.1.1 Brief Summary of Adverse Events

An AE was defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP. Only symptoms/signs that began or worsened in severity after IMP administration were recorded as AEs in the CRF (within the study period, i.e., up to 48 to 96 hours after DaTSCAN™ administration).

Table 37 presents a summary of AEs that occurred during the entire study. Of 179 subjects who were dosed, 122 subjects (68%) reported 400 AEs. Of the 122 subjects reporting AEs, in 42 subjects the maximum intensity was mild, in 51 subjects it was moderate, and in 26 subjects it was severe. For 3 subjects the AE intensity was not reported. A total of 32 subjects (18%) experienced at least 1 SAE, and 10 subjects (6%) had at least 1 AE leading to discontinuation from the study. Four subjects (2%) had AEs that led to death. None of the AEs leading to death were considered by the investigator to be related to administration of DaTSCAN™.

Of the 179 subjects, 13 subjects (7%) had 24 AEs that were considered by the investigator to be related to administration of DaTSCAN™ (Table 37). Of the 13 subjects with related AEs, in 9 subjects the maximum intensity was mild and in 4 subjects it was moderate. None of the related AEs were severe. None of the SAEs were considered by the investigator to be related to administration of DaTSCAN™, and no subject had a related AE that led to discontinuation from the study.

Table 37 Summary of Adverse Events, All Doses, Safety Population

	All Events (N=179) n (%)	Study Drug Related n (%)
Subjects with at least one AE	122 (68)	13 (7)
Number of AEs	400	24
Maximum Intensity[a]		
Mild	42 (23)	9 (5)
Moderate	51 (28)	4 (2)
Severe	26 (15)	0 (0)
Missing	3 (2)	0 (0)
Subjects with at least one SAE	32 (18)	0 (0)
Subjects with at least one AE leading to discontinuation	10 (6)	0 (0)
Deaths	4 (2)	0 (0)

N = number of subjects in the safety population; n = number of subjects in each category; AE = adverse event; SAE = serious adverse event.
Safety population includes subjects who received any amount of DaTSCAN™ and underwent at least 1 safety assessment.
Subjects with more than 1 occurrence in a category are counted once. Percentages are based on N.
'Study drug related' includes AEs reported to have either a suspected or a probable relationship with DaTSCAN™.
[a] Maximum AE severity for each subject is used for tabulation.
REF: Section 14.3, Table [14.3.1.1.1.a].

12.1.2 Display of Adverse Events

In this section, AEs are tabulated by dose number (i.e., first dose, second dose, third dose).

AEs and symptoms that were reported from the time during the T = 0 imaging visit up to and including the T = 18 screening visit were associated with the first dose. AEs and symptoms that were reported from the time during the T = 18 imaging visit up to and including the T = 36 telephone interview were associated with the second dose. AEs and symptoms that occurred after the third dosing during the T = 36 imaging visit were associated with the third dose. The protocol defined duration of safety surveillance was only 7 days following an injection, so the inclusion of all AEs between injections may lead to an overestimation of AE rates.

Only symptoms/signs that began or worsened in severity after IMP administration were recorded as AEs in the CRF (within the study period, i.e., up to 48 to 96 hours after DaTSCAN™ administration).

12.1.2.1 Tabulation of adverse events by dose period

(a) Adverse events, Dose 1 (T = 0)

Table 38 presents a summary of AEs that occurred in association with the first dose of DaTSCAN™ (T = 0). Of 179 subjects who were dosed, 107 subjects (60%) reported 241 AEs. Of the 107 subjects reporting AEs, in 54 subjects the maximum intensity was mild, in 37 subjects it was moderate, and in 13 subjects it was severe. For 3 subjects the AE intensity was not reported. A total of 17 subjects (9%) experienced at least 1 SAE, and 5 subjects (3%) had at least 1 AE leading to discontinuation from the study. Three subjects (2%) had AEs that led to death during the T = 0 time period, which extended up to the T = 18 screening visit. None of the AEs leading to death were considered by the investigator to be related to administration of DaTSCAN™.

Of the 179 subjects dosed at T = 0, 8 subjects (4%) had 12 AEs that were considered by the investigator to be related to administration of DaTSCAN™ (Table 38). Of the 8 subjects with related AEs, in 5 subjects the maximum intensity was mild and in 3 subjects it was moderate. None of the related AEs were severe. None of the SAEs were considered by the investigator to be related to administration of DaTSCAN™, and no subject had a related AE that led to discontinuation from the study.

Table 38 Summary of Adverse Events, First Dose (T = 0), Safety Population

	All Events (N=179) n (%)	Study Drug Related n (%)
Subjects with at least one AE	107 (60)	8 (4)
Number of AEs	241	12
Maximum Intensity[a]		
Mild	54 (30)	5 (3)
Moderate	37 (21)	3 (2)
Severe	13 (7)	0 (0)
Missing	3 (2)	0 (0)
Subjects with at least one SAE	17 (9)	0 (0)
Subjects with at least one AE leading to discontinuation	5 (3)	0 (0)
Deaths	3 (2)	0 (0)

N = number of subjects in the safety population; n = number of subjects in each category; AE = adverse event; SAE = serious adverse event.
Safety population includes subjects who received any amount of DaTSCAN™ and underwent at least 1 safety assessment.
Subjects with more than 1 occurrence in a category are counted once. Percentages are based on N.
'Study drug related' includes AEs reported to have either a suspected or a probable relationship with DaTSCAN™.
[a] Maximum AE severity for each subject is used for tabulation.
REF: Section 14.3, Table [14.3.1.1.1.b].

(b) Adverse events, Dose 2 (T = 18)

Table 39 presents a summary of AEs that occurred in association with the second dose of DaTSCAN™ (T = 18). Of 127 subjects who were dosed, 63 subjects (50%) reported 130 AEs. Of the 63 subjects reporting AEs, in 22 subjects the maximum intensity was mild, in 28 subjects it was moderate, and in 13 subjects it was severe. A total of 18 subjects (14%) experienced at least 1 SAE, and 4 subjects (3%) had at least 1 AE leading to discontinuation from the study. No subject died during the T = 18 time period, which extended up to the T = 36 telephone interview.

Of the 127 subjects dosed at T = 18, 7 subjects (6%) had 10 AEs that were considered by the investigator to be related to administration of DaTSCAN™ (Table 39). Of the 7 subjects with related AEs, in 5 subjects the maximum intensity was mild and in 2 subjects it was moderate. None of the related AEs were severe. None of the SAEs were considered by the investigator to be related to administration of DaTSCAN™, and no subject had a related AE that led to discontinuation from the study.

Table 39 Summary of Adverse Events, Second Dose (T = 18), Safety Population

	All Events (N=127) n (%)	Study Drug Related n (%)
Subjects with at least one AE	63 (50)	7 (6)
Number of AEs	130	10
Maximum Intensity[a]		
Mild	22 (17)	5 (4)
Moderate	28 (22)	2 (2)
Severe	13 (10)	0 (0)
Subjects with at least one SAE	18 (14)	0 (0)
Subjects with at least one AE leading to discontinuation	4 (3)	0 (0)
Deaths	0 (0)	0 (0)

N = number of subjects in the safety population; n = number of subjects in each category; AE = adverse event; SAE = serious adverse event.
Safety population includes subjects who received any amount of DaTSCAN™ and underwent at least 1 safety assessment.
Subjects with more than 1 occurrence in a category are counted once. Percentages are based on N.
'Study drug related' includes AEs reported to have either a suspected or a probable relationship with DaTSCAN™.
[a] Maximum AE severity for each subject is used for tabulation.
REF: Section 14.3, Table [14.3.1.1.1.c].

(c) Adverse events, Dose 3 (T = 36)

Table 40 presents a summary of AEs that occurred in association with the third dose of DaTSCAN™ (T = 36). Of 99 subjects who were dosed, 17 subjects (17%) reported 29 AEs. Of the 17 subjects reporting AEs, in 8 subjects the maximum intensity was mild, in 6 subjects it was moderate, and in 3 subjects it was severe. A total of 3 subjects (3%) experienced at least 1 SAE, and 1 subject (1%) had at least 1 AE leading to discontinuation from the study. One subject (1%) died during the T = 36 time period. None of the AEs leading to the single death were considered by the investigator to be related to administration of DaTSCAN™.

Of the 99 subjects dosed at T = 36, 2 subjects (2%) had 1 AE each that was considered by the investigator to be related to administration of DaTSCAN™ (Table 40). Of the 2 subjects with related AEs, in 1 subject the maximum intensity was mild and in 1 subject it was moderate. None of the related AEs were severe. None of the SAEs were considered by the investigator to be related to administration of DaTSCAN™, and no subject had a related AE that led to discontinuation from the study.

Table 40 Summary of Adverse Events, Third Dose (T = 36), Safety Population

	All Events (N=99) n (%)	Study Drug Related n (%)
Subjects with at least one AE	17 (17)	2 (2)
Number of AEs	29	2
Maximum Intensity[a]		
Mild	8 (8)	1 (1)
Moderate	6 (6)	1 (1)
Severe	3 (3)	0 (0)
Subjects with at least one SAE	3 (3)	0 (0)
Subjects with at least one AE leading to discontinuation	1 (1)	0 (0)
Deaths	1 (1)	0 (0)

N = number of subjects in the safety population; n = number of subjects in each category; AE = adverse event; SAE = serious adverse event.
Safety population includes subjects who received any amount of DaTSCAN™ and underwent at least 1 safety assessment.
Subjects with more than 1 occurrence in a category are counted once. Percentages are based on N.
'Study drug related' includes AEs reported to have either a suspected or a probable relationship with DaTSCAN™.
[a] Maximum AE severity for each subject is used for tabulation.
REF: Section 14.3, Table [14.3.1.1.1.d].

(d) All doses

A summary of AEs that occurred during the entire study is presented in Section 12.1.1.

12.1.2.2 Adverse events by system organ class and preferred term

(a) All adverse events

Of 179 subjects who received at least 1 dose of DaTSCAN™ during the study, 122 subjects (68%) reported 400 AEs. The most common System Organ Class (SOC) in which AEs occurred was nervous system disorders (53 subjects, 30%), followed by musculoskeletal and connective tissue disorders (41 subjects, 23%), infections and infestations (34 subjects, 19%), gastrointestinal disorders (30 subjects, 17%), vascular disorders (18 subjects, 10%), respiratory disorders (15 subjects, 8%), and injury, poisoning and procedural complications (14 subjects, 8%). For all other SOCs the frequency of AEs was ≤7%.

The most common AE was headache (26 subjects, 15%), followed by dizziness (12 subjects, 7%), arthralgia and nasopharyngitis (9 subjects each, 5%), and nausea and hypertension (8 subjects each, 4%). All other AEs occurred in ≤7, or ≤4% of subjects.

Table 41 presents, by SOC and preferred term (PT), a summary of AEs that occurred in ≥2% of subjects, along with a count of the number of AEs. A complete tabulation of AEs, by SOC and PT, showing the number and percentage of subjects experiencing each AE, along with a count of AEs, may be found in Section 14.3, Table [14.3.1.1.2].

Table 41 Adverse Events Occurring in ≥2% of Subjects, by System Organ Class and Preferred Term – Safety Population

	All Events (N=179)	
System Organ Class / Preferred Term[a]	Number of Subjects n (%)	Number of Events
Subjects with at least one AE	122 (68%)	400
Blood and lymphatic system disorders /		
Any	6 (3%)	6
Anaemia	4 (2%)	4
Cardiac disorders /		
Any	11 (6%)	12
Eye disorders /		
Any	7 (4%)	8
Gastrointestinal disorders /		
Any	30 (17%)	43
Constipation	4 (2%)	4
Diarrhoea	5 (3%)	6
Dry mouth	3 (2%)	3
Nausea	8 (4%)	9
General disorders and administration site conditions /		
Any	11 (6%)	14
Chest pain	3 (2%)	3
Infections and infestations /		
Any	34 (19%)	48
Influenza	5 (3%)	6
Lower respiratory tract infection	5 (3%)	6
Nasopharyngitis	9 (5%)	12
Pneumonia	3 (2%)	3
Urinary tract infection	4 (2%)	4

Table 41 Adverse Events Occurring in ≥2% of Subjects, by System Organ Class and Preferred Term – Safety Population

System Organ Class / Preferred Term[a]	All Events (N=179)	
	Number of Subjects n (%)	Number of Events
Injury, poisoning and procedural complications /		
Any	14 (8%)	21
Fall	6 (3%)	8
Investigations /		
Any	7 (4%)	7
Metabolism and nutrition disorders /		
Any	8 (4%)	14
Diabetes mellitus	3 (2%)	4
Hypercholesterolaemia	4 (2%)	4
Musculoskeletal and connective tissue disorders /		
Any	41 (23%)	61
Arthralgia	9 (5%)	9
Arthritis	3 (2%)	4
Back pain	7 (4%)	7
Muscle spasms	4 (2%)	5
Myalgia	3 (2%)	3
Neck pain	7 (4%)	7
Pain in extremity	6 (3%)	6
Spinal osteoarthritis	4 (2%)	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps) /		
Any	7 (4%)	8
Nervous system disorders /		
Any	53 (30%)	80
Balance disorder	4 (2%)	5
Dizziness	12 (7%)	16
Headache	26 (15%)	33
Lethargy	3 (2%)	3
Tremor	6 (3%)	6
Psychiatric disorders /		
Any	13 (7%)	13
Depression	5 (3%)	5
Renal and urinary disorders /		
Any	5 (3%)	5
Respiratory, thoracic and mediastinal disorders /		
Any	15 (8%)	16
Skin and subcutaneous tissue disorders /		
Any	6 (3%)	7
Rash	3 (2%)	4
Surgical and medical procedures /		
Any	7 (4%)	9
Vascular disorders /		
Any	18 (10%)	20
Hypertension	8 (4%)	9

N = number of subjects in the safety population; n = number of subjects in each category; AE = adverse event.
Safety population includes subjects who received any amount of DaTSCAN™ and underwent at least one safety assessment.
Subjects with more than one occurrence in a category are counted once. Percentages are based on N.
'Study drug related' includes AEs reported to have either a suspected or a probable relationship with DaTSCAN™.
[a] Medical Dictionary for Regulatory Activities (MedDRA) Version 11.0.
REF: Section 14.3, Table [14.3.1.1.2].

(b) Related adverse events

Twenty-four AEs that were considered by the investigator to be related to administration of DaTSCAN™ occurred in 13 subjects (7%; Table 42). The most common related AE was headache (5 subjects, 3%), followed by nausea (3 subjects, 2%), injection site hematoma, dizziness, and dysgeusia (2 subjects each, 1%). All other related AEs occurred in 1 subject (<1%) each.

Table 42 Related Adverse Events, by System Organ Class and Preferred Term – Safety Population

System Organ Class / Preferred Term[a]	All Events (N=179)		Study Drug Related	
	Number of Subjects n (%)	Number of Events	Number of Subjects n (%)	Number of Events
Subjects with at least one AE	122 (68%)	400	13 (7%)	24
Ear and labyrinth disorders /				
Any	2 (1%)	3	1 (<1%)	1
Ear pain	1 (<1%)	1	1 (<1%)	1
Gastrointestinal disorders /				
Any	30 (17%)	43	4 (2%)	5
Dry mouth	3 (2%)	3	1 (<1%)	1
Nausea	8 (4%)	9	3 (2%)	3
Toothache	1 (<1%)	1	1 (<1%)	1
General disorders and administration site conditions /				
Any	11 (6%)	14	3 (2%)	4
Injection site haematoma	2 (1%)	3	2 (1%)	3
Injection site pain	1 (<1%)	1	1 (<1%)	1
Metabolism and nutrition disorders /				
Any	8 (4%)	14	1 (<1%)	2
Increased appetite	1 (<1%)	2	1 (<1%)	2
Musculoskeletal and connective tissue disorders /				
Any	41 (23%)	61	1 (<1%)	1
Neck pain	7 (4%)	7	1 (<1%)	1
Nervous system disorders /				
Any	53 (30%)	80	9 (5%)	10
Dizziness	12 (7%)	16	2 (1%)	2
Dysgeusia	2 (1%)	2	2 (1%)	2
Headache	26 (15%)	33	5 (3%)	5
Somnolence	1 (<1%)	1	1 (<1%)	1
Vascular disorders /				
Any	18 (10%)	20	1 (<1%)	1
Hypertension	8 (4%)	9	1 (<1%)	1

N = number of subjects in the safety population; n = number of subjects in each category; AE = adverse event.
Safety population includes subjects who received any amount of DaTSCAN™ and underwent at least one safety assessment.
Subjects with more than one occurrence in a category are counted once. Percentages are based on N.
'Study drug related' includes AEs reported to have either a suspected or a probable relationship with DaTSCAN™.
[a] Medical Dictionary for Regulatory Activities (MedDRA) Version 11.0.
REF: Section 14.3, Table [14.3.1.1.2].

(c) Adverse events by intensity

Of the 179 subjects who received at least 1 dose of DaTSCAN™, 42 subjects (23%) had 210 AEs with a maximum intensity of mild, 51 subjects (28%) had 104 AEs with a maximum intensity of moderate, and 26 subjects (15%) had 43 AEs with a maximum intensity of severe.

Nine subjects (5%) had 14 related AEs with a maximum intensity of mild and 4 subjects (2%) had 8 AEs with a maximum intensity of moderate. No subject had a severe AE that was related to treatment with DaTSCAN™.

The 8 moderate AEs that were considered by the investigator to be related to treatment with DaTSCAN™ were: headache (4 events), and ear pain, toothache, increased appetite, and neck pain (1 event each).

A summary of all AEs and related AEs, by SOC and PT and by maximum intensity, may be found in Section 14.3, Table [14.3.1.1.3].

12.1.3 Analysis of Adverse Events

A descriptive analysis only was performed for AEs.

The AE profile was reviewed to look for any of the known effects of cocaine. The known effects of cocaine are nervousness, restlessness, excitement, euphoria, hallucinations, tachypnea, bradycardia at low doses, tachycardia at moderate doses, hypertension, vomiting due to CNS stimulation, tremors, and seizures [McEvoy, 2005]. A few of the 179 subjects had AEs that are known side effects of cocaine: 8 subjects had hypertension, 6 subjects had tremors, 1 subject had a hallucination and 1 subject had vomiting. Of these, 1 case of hypertension (<1% of subjects) was attributed to DaTSCAN™ by the investigator. There were 9 reported cases of nausea (4 % of subjects), of which 3 were reported as related to DaTSCAN™.

12.1.4 Listing of Adverse Events by Subject

A listing of all AEs by subject was not produced for this report. A listing of deaths by subject can be found in Section 14.3, Table [14.3.2.1], a listing of SAEs by subject can be found in Section 14.3, Table [14.3.2.2], and a listing of subjects who were discontinued from the study due to an AE can be found in Section 14.3, Table [14.3.2.3].

12.2 Deaths and Other Serious or Significant Adverse Events

12.2.1 Deaths

Four subjects died during the study. These 4 subjects experienced a total of 14 AEs. All of the deaths were deemed by the investigator to be not related to DaTSCAN™ or to any other study procedure.

The deaths of 3 of the subjects occurred 7.5 months, 16 months, and approximately 12 months after a single dose of DaTSCAN™ had been administered at the T = 0 time point. Brief narratives for these 3 subjects are provided below.

(1) Subject 01-0122 was a 71-year-old (at T = 0 screening) female diagnosed as having possible ET at study entry and with a medical history including glaucoma, arthritis, and hypertension. Concomitant medication included: timolol maleate, brimonidine titrate, amlodipine, bendrofluazide, cod liver oil, and paracetamol. Medical history included glaucoma, arthritis, and hypertension. The subject received 1 injection of DaTSCAN™ (127 MBq) on 25 September 2001 (batch 01J24FP). While attempting to contact the subject to schedule her 18-month screening visit, the investigator was informed that the subject had been hospitalized on 04 January 2003 and died the same day (16 months after receiving the study drug). The death was deemed to be unrelated to DaTSCAN™ or to any study procedure. Bronchial carcinoma was reported to be the cause of death.

(2) Subject 04-0401 was an 86-year-old male diagnosed as having early Parkinsonism and with a medical history including pemphigoid and prostatic hypertrophy. Concomitant medications included prednisolone, fucicort, loratadine, tamsulosin MR, and senna. The subject received 1 injection of DaTSCAN™ (181 MBq) on 28 August 2001 (batch 01H27FP). On 04 April 2002, 7.5 months after receiving DaTSCAN™, the subject had a fall which led to a fracture of the neck of the femur. Five days later, the subject underwent hemiarthroplasty. The subject developed left ventricular failure post-operatively on 09 August 2002. Ischemic heart disease was reported with onset 10 April 2002. The patient gradually deteriorated and died 3 days later on 13 April 2002. The investigator deemed all events and the death to be unrelated to DaTSCAN™ or to any study procedures. The cause of death was reported to be cardio-respiratory failure secondary to fracture of femoral neck.

(3) Subject 06-0612 was a 74-year-old (at T = 0 screening) female subject diagnosed as having early Parkinsonism and with a medical history including Raynaud's syndrome, urinary retention, chronic constipation, carpal tunnel syndrome, chronic lumbalgia, degenerative arthroplasty, Paget's disease, cholecystectomy, and appendectomy. Concomitant medication included: Lugol's solution (aqueous iodine solution), pramipexole dihydrochloride, levodopa, carbidopa. The subject received 1 injection of DaTSCAN™ (184 MBq) on 26 March 2002 (batch 02C25D). According to a telephone report received on 07 October 2003, the patient died due to generalized septicemia on 03 April 2003 (approximately 12 months after the DaTSCAN™

injection). The investigator deemed this event to be unrelated to DaTSCAN™ or to any other study procedure.

The death of the fourth subject occurred 1 year after the second dose of DaTSCAN™ had been administered at the T = 18 time point. A brief narrative for this subject is provided below.

(4) Subject 04-0400 was a 73-year-old male subject diagnosed as having early Parkinsonism with a medical and surgical history of pyloric stenosis, amoebic dysentery, diabetes mellitus, ischemic heart disease, prostatic hypertrophy, and ileostomy. Concomitant medication included: pramipexole, tramadol, soluble aspirin, nicorandil, diazepam, loperamide, frusemide, ramipril, bisoprolol, finasteride, spironolactone, porcine insulatard, codydramol (paracetamol with codeine), simvastatin, morphine sulfate (Oramorph), warfarin, enoxaparin sodium, amoxicillin with clavulanate potassium (Co-Amoxiclar), morphine, enoxaparin sodium (Clexane), cyclizine, metoclopramide, pramipexole, ciprofloxacin, lansoprazole, digoxin, modopar, perindopril, prochlorperazine, ranitidine, erythromycin, amoxicillin, clavulin (Augmentin), diamorphine, and codeine phosphate.

The subject was given DaTSCAN™ on 2 occasions: 28 August 2001 (177.2 MBq, batch 01H27FP) and 08 April 2003 (171.6 MBq, batch 03D07D).

Approximately 5.5 months after the second injection of DaTSCAN™, on 18 September 2003, the subject was hospitalized with abdominal pain. While in the hospital, the subject developed several events, which were all classified as non-serious: deep vein thrombosis, as well as infection of the chest, the left elbow, and the left big toe. The abdominal pain resolved on 17 November 2003. The subject was discharged home on 10 December 2003 with an ongoing infection of the toe and the elbow. The investigator deemed all of these events to be not related to the administration of DaTSCAN™ or to any other study procedure.

Two weeks later, on 24 December 2003, the subject was re-admitted to the hospital with abdominal distention, reduced ileostoma output, and vomiting. Both the abdominal distention and the vomiting were classified as serious. The subject was discharged on 26 December 2003, with the events resolved. The investigator deemed these events to be not related to DaTSCAN™.

Subsequently, the subject developed urinary tract infection (non-serious) on 06 February 2004, which resolved. On 13 February 2004, the subject was hospitalized with pneumonia, classified as serious. The subject died 2 months later on 19 April 2004; cause of death was reported to be respiratory failure. The investigator reported that the subject had been an insulin-dependent diabetic for many years and had been increasingly ill for the past 6 months with repeated chest infections, ischemic heart disease, and severe peripheral vascular disease with gangrenous toes. Neither the pneumonia nor the subject's death was judged by the investigator to be related to DaTSCAN™ or to any other study procedures.

12.2.2 Other Serious Adverse Events

Over the entire study period a total of 32 subjects experienced 71 SAEs (symptoms reported at the T = 18 and T = 36 screening visits and classified as serious were also included). All of these SAEs/symptoms were deemed to be not related to DaTSCAN™ or to any other study procedure. The majority of the SAEs (58 SAEs, 81.6%) were reported as resolved, 7 SAEs (9.9%) as ongoing and 6 SAEs (8.5%, in 4 subjects) with a fatal outcome. A listing of SAEs that occurred in the safety population during the study period is provided in Section 14.3, Listing [14.3.2.2].

Complete narratives for these SAEs are presented in Section [14.3.3].

12.2.3 Other Significant Adverse Events

A significant AE was defined as any non-serious AE that comprised an abnormal clinical laboratory test result, or any AE that led to an intervention including withdrawal of IMP treatment, dose reduction, or the addition of significant therapeutic intervention.

Ten subjects were discontinued from the study as a result of AEs. None of these AEs were considered by the investigator to be related to treatment with DaTSCAN™. A listing of subjects who were discontinued from the study as a result of AEs is provided in Section 14.3, Listing [14.3.2.3].

One subject (subject 06-0609, 85-year-old male) experienced a significant AE of thrombocytopenia ("platelet count decreased") during the T = 0 post-imaging follow-up visit, that was deemed to be mild and unlikely to be related to DaTSCAN™. Corrective therapy was not administered; the final outcome of the event was "ongoing".

12.2.4 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

As none of the deaths and SAEs was deemed by the investigators to be related to DaTSCAN™, the review of the events did not reveal any safety signals.

12.3 Clinical Laboratory Evaluation

Clinical laboratories (serum biochemistry, hematology, and urinalysis) were measured at 2 time points before administration and once after administration of DaTSCAN™ (24 to 72 hours). Clinical laboratory data were reviewed for trends and/or safety signals. Hematology parameters included hematocrit, hemoglobin, platelets, erythrocytes, leukocytes, neutrophils, eosinophils, basophils, lymphocytes, monocytes, and prothrombin time. Serum biochemistry included sodium, potassium, creatinine, blood urea nitrogen, bilirubin, albumin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyltransferase, lactate dehydrogenase, creatinine phosphokinase, creatinine phosphokinase-MB fraction, and creatinine phosphokinase-MM fraction. Urinalysis included a

dipstick for specific gravity, leukocytes, pH, albumin, glucose, ketones, urobilinogen, bilirubin, and hemoglobin, as well as a microscopic examination for white blood cells, red blood cells, crystals, casts, epithelial cells, and bacteria.

All laboratory parameters showed general stability over time, and no clinically significant mean changes from baseline or trends indicative of safety concerns were noted. Detailed results of the evaluation of clinical laboratory tests may be found in Section [12.3] of the European PDT304 CSR.

12.4 Vital Signs

Vital-sign evaluations comprised systolic/diastolic BP and PR. Pre-administration measurements were taken at the T = 0 screening and during the T = 0 imaging visit prior to DaTSCAN™ administration (i.e., baseline value). Following the first injection of DaTSCAN™, vital signs were measured within 4 to 7 hours post-injection and at the 24 to 72 hours follow-up visit. During the T = 18 and T = 36 imaging visit measurements were taken prior to DaTSCAN™ administration (i.e., baseline value) and within 4 to 7 hours post-injection.

When comparing baseline to post-baseline measurements, systolic and diastolic BP, and PR measurements for all subjects showed overall stability after all injections of DaTSCAN™. No significant trends indicative of a safety concern were apparent. Detailed results of the evaluation of vital signs may be found in Section [12.4] of the European PDT304 CSR.

12.5 Electrocardiogram

12-lead ECGs were recorded and evaluated at T = 0 screening and during the T = 0 post imaging follow-up visit (24 to 72 hours post injection). ECGs were not recorded after the second and third injection of DaTSCAN™. The ECGs were reviewed by the investigator for any occurrence of abnormal rhythm changes from baseline. ECG intervals were not recorded or statistically analyzed.

Review of individual subject data sets did not indicate any safety signals or trends worthy of more detailed investigation. There were no post-baseline ECGs having demonstrated prolonged intervals. Detailed results of the evaluation of ECG data may be found in Section [12.5] of the European PDT304 CSR.

12.6 Physical Examination

A physical examination was conducted at T = 0 screening, T = 0 imaging prior to DaTSCAN™ administration, and at the T = 0 post-imaging follow-up (24 to 72 hours post-injection). The examination included assessments for the presence of abnormalities of the following: general condition, respiratory tract, urogenital system, cardiovascular, gastrointestinal, nervous system, musculoskeletal, skin, hematological system and lymph nodes, and endocrine system. Post-injection findings were classified by the investigator as either "normal" or "abnormal." There

were no post-baseline changes that were deemed clinically significant. The majority of the findings at post dosing time points were also present at baseline. Detailed results of the evaluation of physical examination findings may be found in Section [12.6] of the European PDT304 CSR.

12.7 Injection Site Reactions

Injection site reactions were not specifically collected in this study but such reactions were collected within the scope of AEs. A total of 3 subjects (1.7%) reported injection site AEs. Subject 01-0135 (67-year-old male) experienced mild injection site pain 24 hours after the first injection that was deemed probably related to DaTSCAN™. The event resolved within 6 hours. An additional 2 subjects (subject 02-0065, a 62-year-old male; subject 02-0067, a 77-year-old female) experienced mild hematoma. Both of these reactions were deemed probably related to DaTSCAN™. At last report, the hematoma for subject 02-0065 was ongoing and the hematoma for subject 02-0067 had resolved. All 3 of the subjects who experienced injection site reactions received their second injection of DaTSCAN™ without incident.

12.8 Safety Conclusions

- Among the 179 subjects in the safety population, 122 subjects (68%) experienced a total of 400 AEs. Of these, 32 subjects (18%) experienced 71 non-fatal SAEs. Four subjects (2%) experienced SAEs that resulted in death: 1 related to bronchial carcinoma, 1 the result of cardio-respiratory failure after hip fracture, 1 caused by septicemia and the fourth to respiratory failure secondary to multi-morbidity. None of the SAEs were deemed to be related to DaTSCAN™.

  The majority of the AEs (376 AEs, 94%) were deemed by the investigator not to be related to DaTSCAN™. The most frequently reported AE was headache (15% of subjects).

  Only 24 AEs (6%) were considered as having reasonable relationship to DaTSCAN™, most of which were mild in intensity (14, 3.5%). The most common AEs for which the investigator believed there to be a relationship to DaTSCAN™ were: headache (5 subjects, 3%), followed by nausea (3 subjects, 2%), injection site hematoma, dizziness, and dysgeusia (2 subjects each, 1%).

  Other than 8 subjects with hypertension, 8 subjects with nausea, 6 subjects with tremors, 1 subject with hallucination and 1 subject with vomiting, there were no AEs suggestive of cocaine-like effects. This is consistent with the low mass dose of [^{123}I]FP-CIT.

  As reported in the European CSR:

- All laboratory values for serum biochemistry, hematology, and urinalysis data showed general stability over time with no clinically significant mean changes from baseline or trends indicative of a safety concern.

- Group mean values for vital signs showed stability over time when compared to baseline. No significant trends indicative of a safety concern were apparent.

- No significant effects of DaTSCAN™ administration on ECG waveform were detected. None of the observed ECG waveform abnormalities were accompanied by changes in subject management. ECG intervals were not measured. In summary, no ECG abnormalities or trends indicative of a safety signal were detected.

- Changes in physical examination after DaTSCAN™ administration were infrequent, minor and were not accompanied by changes in subject management or by AEs.

13 DISCUSSION AND OVERALL CONCLUSIONS

13.1 Efficacy Discussion

The diagnostic assessment of patients with movement disorder symptoms such as tremor, bradykinesia, and rigidity depends on clinical examination, and it is aimed at determining whether the patient has PD or a similar PS, or a non-Parkinsonian disorder (e.g., ET). What differentiates these disorder pathologically is the presence or absence of a SDD, i.e., a loss of dopaminergic nigrostriatal neurons, which is associated with PS (e.g., PD), but not with non-PS disorders such as ET.

The vulnerability and relative inaccessibility of the brain makes biopsy impractical as a diagnostic method, so the differentiation between these disorders is usually based on clinical criteria such as those of the UK Brain Bank. However, studies using the UK Brain Bank criteria and including pathological confirmation have verified that PD (which involves a SDD) is misdiagnosed by specialists in up to 25% of cases [Hughes et al. 2001]. In addition, retrospective studies have shown that up to 29% of patients initially diagnosed with PD by primary physicians received an alternative diagnosis upon re-examination by a MDS [Reich et al. 2002]. ET is a non-SDD associated movement disorder that is frequently mistaken clinically for PD in the early stages, with a reported misdiagnosis rate of approximately 25% [Quinn 1995].

The PDT304 study not only served to fulfill a post-approval commitment to the EMEA, but also verified the efficacy of DaTSCAN™ imaging in the detection or exclusion of a SDD in patients with symptoms and signs of movement disorders (such as ET or early PD). One of the main strengths of this study was the long period of follow-up (36 months) to establish the SOT diagnosis. Other study strengths include a blinded read (with 3 independent readers) and a robust SOT. A limitation was the large percentage of subjects who did not complete the trial. For the primary efficacy analysis, DaTSCAN™ SPECT findings acquired upon subject entry into the trial (T = 0) were compared to the SOT assessment of striatal status (SDD or no SDD), which was based on the consensus expert clinical diagnosis of 2 independent MDS 3 years later (SOT at T = 36).

The sensitivity of DaTSCAN™ SPECT in the detection or exclusion of a SDD at T = 0 was 77.5% to 78.6% (depending upon the blinded reader; the mean across all 3 readers was 77.99%); the specificity was 96.8% for each reader. Furthermore, the ability of DaTSCAN™ SPECT imaging to detect or exclude a SDD in patients with movement disorders early on was underscored by the increased convergence between the BIE image findings and the SOT diagnoses over the course of 3 years, as well as by the stability of (e.g., minimal change in) SPECT findings over the 3 imaging time points (i.e., 0, 18, and 36 months).

A particular strength clearly demonstrated by DaTSCAN™ SPECT in the present study is its high specificity. In contrast, the specificity of the on-site physician's initial diagnosis (T = 0) was only 51.6% when compared to the final SOT at T = 36. A similar low specificity (30%) was reported by Jennings et al. in a study of 35 subjects with clinically uncertain PS

[Jennings et al. 2004]; the low specificity indicates a high false positive rate among the participating community neurologists.

Our findings together with those in the literature [Jennings et al. 2004, Reich et al. 2002] indicate that in routine clinical practice there is a definite tendency toward over-diagnosis which may result in inappropriate initiation of treatment of non-PD (non-SDD) patients with anti-Parkinson's medication. In contrast the high specificity of DaTSCAN™ SPECT indicates that if a SPECT finding is abnormal the clinician can be very confident that the diagnosis of a SDD is correct. Thus, by avoiding over-diagnosis, the clinician can avoid inappropriate therapy with anti-Parkinson's agents (e.g., levodopa, dopamine agonists) as well as potentially serious side effects. Furthermore, a definitive diagnosis allows the patient and their family to better understand the disease and facilitates future planning. It should also be noted that in the case of misdiagnosis significant resources are spent on CT and MR imaging of the brain to rule out other less likely etiologies of PD and PS [Jennings et al. 2004].

The usefulness of DaTSCAN™ imaging in routine clinical practice is supported by the high inter-reader agreement for the visual assessment between the independent blinded SPECT readers as well as the on-site SPECT readers, as indicated by high values of Cohen's κ. Not only was there a good agreement across readers, but the DaTSCAN™ image findings were also remarkably stable over time, that is, the classification as to normal or abnormal image did not change over the 3 imaging time points over 3 years.

13.2 Safety Discussion

In support of previous findings, the results of the present study indicate DaTSCAN™ to be a safe and well-tolerated radiopharmaceutical. Of the 71 SAEs that occurred in 32 subjects (with 4 subjects experiencing fatal SAEs), none were deemed by the investigator to be related to DaTSCAN™. There was no specific profile for any occurring AEs. Those reported were primarily mild in intensity and resolved during the study. Only 24 of the non-serious AEs (6%) were considered to be related to DaTSCAN™: headache (5 subjects, 3%), followed by nausea (3 subjects, 2%), injection site hematoma, dizziness, and dysgeusia (2 subjects each, 1%). Assessment of laboratory parameters for hematology, serum biochemistry, and urinalyses, as well as vital signs and ECGs revealed no trends or signals over time indicative of a safety concern. Changes in physical examination and injection site were not deemed to be a safety concern and in most cases, changes in the latter were not related to DaTSCAN™ administration.

13.3 Overall Conclusions

Despite significant advancements in our understanding of the pathophysiology of the various types of movement disorders there is no widely accepted biomarker for any of these diseases. Practicing neurologists and research investigators therefore continue to rely on clinical diagnosis, which often has high sensitivity at the expense of specificity because of the over-diagnosis of PS (which involves a SDD). The results of the present trial verify that DaTSCAN™ can detect or exclude the presence of a SDD (i.e., loss of dopaminergic

nigrostriatal neurons) in patients with symptoms and signs of movement disorders. This may help the clinician avoid false positive diagnoses and the initiation of inappropriate therapy (e.g., administration of levodopa or dopamine agonists in non-SDD patients). The high inter-reader agreement rate verifies the robustness of DaTSCAN™ SPECT visual assessment, as does the stability of the findings over time.

Among the 179 dosed subjects evaluated for safety, there was overall stability through the follow-up period for all parameters, including clinical laboratory, vital signs, and ECG. No clinically important safety signals or trends over time were noted.

Overall, the results of this 3-year follow-up study verify DaTSCAN™ to be a safe, well-tolerated, robust, reproducible, and useful tool for providing objective evidence about the integrity of the dopaminergic nigrostriatal neurons. Using DaTSCAN™, physicians can learn whether or not a patient has a SDD. This information, when added to the usual clinical information currently collected during patient assessment, can help physicians narrow the differential diagnosis for patients with the symptoms and signs of movement disorders. This may help them reach a more accurate diagnosis earlier, which will allow appropriate treatment to be started earlier, possibly resulting in improved quality of life for the patient. In addition, it will help avoid the initiation of treatments which may be ineffective or deleterious.

14 TABLES AND FIGURES REFERRED TO BUT NOT INCLUDED IN THE TEXT

[14.1] Demographic Data Tables and Figures

[14.2] Efficacy Data Tables and Figures

[14.3] Safety Data Tables and Figures

[14.3.1] Displays of Adverse Events

[14.3.2] Listings of Deaths, Serious and Other Significant Adverse Events

[14.3.3] Narratives of Deaths, Serious and Other Significant Adverse Events

15 REFERENCE LIST

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16 APPENDICES

16.1 Study Information

[16.1.1] Protocol and Amendments
[16.1.2] Sample Case Report Form
[16.1.3] List of IECs and Representative Written Information for Subjects, and Sample Consent Forms
[16.1.4] List of Investigators and Other Study Personnel, and Curricula Vitae
[16.1.5] Signatures Pages
[16.1.6] Listing of Subjects Receiving Each Batch of Investigational Medicinal Product(s)
[16.1.7] Randomization Scheme and Codes
[16.1.8] Audit Certificates
[16.1.9] Documentation of Statistical Methods
[16.1.10] Documentation of Inter-Laboratory Standardization and Methods and Quality Assurance Procedures
[16.1.11] Publications Based on the Study
16.1.12 Copies of Important Publications Referenced in the Report (Refer to Section [15])

16.2 Subject Data Listings

Not presented.

16.3 Case Report Forms Submitted

[16.3.1] CRFs for Deaths, Other Serious Adverse Events, and Withdrawals for Adverse Events

16.3.2 Other CRFs Submitted

Not presented

16.4 Individual Subject Data Listings

Not presented.

J

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022454

COMPLETE RESPONSE

GE Healthcare
Attention: Allison Mueller
Director, Global Regulatory Affairs
101 Carnegie Center
Princeton, NJ 08540-6231

Dear Ms. Mueller:

Please refer to your new drug application (NDA) dated March 6, 2009, received March 9, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DaTscan (Ioflupane I 123 Injection) for Intravenous Use.

We acknowledge receipt of your amendments dated March 25; April 16 and 22; May 20; June 19; July 7 and 29; August 11, 21, and 27; September 3 and 4; November 18; and December 17, 2009.

The October 26, 2009, amendment constituted a complete response to our September 8, 2009 action letter.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

CLINICAL

The proposed package insert (received on December 17, 2009) did not include the text necessary to support the approval of a controlled substance.

a. Supply a revised label that incorporates this text.

b. Alternatively, verify that this text does not apply to DaTscan, based upon findings from the Drug Enforcement Administration.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

POSTMARKETING ISSUES

Several issues pertinent to clarifying the safety or efficacy of this product require additional information that may be obtained from postmarketing studies or clinical trials. We understand that you are refining your clinical development plans, in response to our letter of September 8, 2009. We reiterate our postmarketing requests from that letter. Specifically, we request that you propose studies and/or clinical trials to address the following issues:

1) To conduct a clinical trial that assesses the agreement between DaTscan imaging results and diagnostic outcomes among non-Caucasian and Caucasian patients. The trial will be designated and conducted in a manner that allows a comparison of the results between the non-Caucasian and Caucasian patients.

2) To conduct a clinical trial that assesses the impact of dopaminergic drugs upon DaTscan results. In addition to any other drugs, levodopa and carbidopa effects should be studied in this trial.

Describe your plans to address the above issues in sufficient detail to permit our evaluation of the adequacy of the proposals. Your response should include:

- A detailed protocol or, at a minimum, a detailed outline describing all design features of the study including sample size and justification, eligibility criteria with rationale, dosing regimens and duration, clinical assessments to be performed and their timing, and endpoints to be analyzed.

- The proposed schedule for conducting the study/clinical trial, including all major milestones for the study/clinical trial, e.g., submission to the FDA of the finalized protocol, initiation of an animal or clinical study, completion of patient accrual, completion of the study/clinical trial, and submission of the final report, with accompanying SAS datasets and applicable revised labeling.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call James Moore, Regulatory Project Manager, at (301) 796- 2050.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22454	ORIG-1	GE HEALTHCARE INC	DA TSCAN

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES W MOORE
12/23/2009

RAFEL D RIEVES
12/23/2009
On behalf of Dr. Pazdur

K

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-454

NDA APPROVAL

GE Healthcare
Attention: Allison Mueller
Head of Americas, Regulatory Affairs
101 Carnegie Center
Princeton, NJ 08540-6231

Dear Ms. Mueller:

Please refer to your New Drug Application (NDA) dated March 6, 2009, received March 9, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for DaTscan (Ioflupane I 123) Injection.

We acknowledge receipt of your amendments dated November 16, December 30, 2010, January 6, and 12, 2011.

The November 16, 2010, submission constituted a complete response to our December 23, 2009, action letter.

This new drug application provides for the use of DaTscan (Ioflupane I 123) Injection for striatal dopamine transporter visualization using single photon emission computed tomography (SPECT) brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian Syndromes (PS).

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your January 12, 2011, submission containing final printed carton and container labels.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable and because the disease/condition does not exist in children.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment, which you agreed to conduct in your November 16, 2010 submission:

> 1725. To conduct a clinical trial that assesses the agreement between DaTscan imaging results and diagnostic outcomes among non-Caucasian and Caucasian patients. This trial will be designed and conducted in a manner that allows a comparison of the results between the non-Caucasian and Caucasian patients.

The timetable you submitted on December 30, 2010, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	December 31, 2011
Trial Completion:	April 30, 2013
Final Report Submission:	July 31, 2013

Our letters of September 8, 2009, and December 23, 2009, identified several issues pertinent to clarifying the safety or efficacy of your product. We previously asked you to propose a clinical trial to assess the impact of dopaminergic drugs upon DaTscan image results. The information you supplied in your November 16, 2010, submission resolved our issues pertinent to the need for this clinical trial. Hence, we do not request a post-marketing commitment for this trial.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment

instructions and program description details at
http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call James Moore, Regulatory Project Manager, at (301) 796-2050.

Sincerely,

{See appended electronic signature page}

Charles Ganley, M.D.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

2.0 SYNOPSIS

Name of Company: Nycomed Amersham plc	Individual Study Table Referring to Part of the Dossier Volume:	*(For National Authority Use Only)*
Name of Finished Product: [^{123}I]FP-CIT Injection		
Name of Active Substance: [^{123}I]-Ioflupane	Page:	

Title of Study:
A single centre, open study of an intravenous dopamine transporter ligand, containing 111MBq [^{123}I]FP-CIT, in healthy volunteers and patients with Parkinson's disease to examine uptake kinetics in various brain regions and safety.

Investigators:
Professor Eric van Royen, MD PhD
Dr. Jan Booij

Study Centre(s):
Department of Nuclear Medicine, Academic Medical Centre, Meibergdreef 9, NL-1105 AZ Amsterdam Z.O., The Netherlands

Publication (reference):
J. Nucl. Med. 1998; 39: 13P (Abstract)

Study Period (months):	2	Phase of Development:
Date of first enrolment:	January 7th, 1997	
Date of last completed:	March 21st, 1997	Phase II

Objectives:
1. To investigate the time course of the uptake of [^{123}I]FP-CIT in various brain regions following a single intravenous injection.
2. To demonstrate differences in striatal uptake of [^{123}I]FP-CIT as determined by SPECT analysis between Parkinson's disease patients and healthy volunteers over a period of 6 hours post-injection.
3. To assess safety and tolerability parameters following [^{123}I]FP-CIT administration.
4. To provide a basis for estimation of sample size calculations for subsequent studies, i.e. Phase III studies.

Methodology:
Single centre, parallel group, open, controlled, non-randomised phase II study.

Number of Subjects (planned and analysed):
A total of 30 subjects (10 healthy volunteers and 20 Parkinson's disease patients) were planned and analysed in this study.

Diagnosis and main criteria for inclusion:
1. Male and female non-patient volunteers with an age appropriate health condition, aged 40-70 years.
2. Male and female patients diagnosed with Idiopathic Parkinson's disease aged 40-70 years.

Name of Company: Nycomed Amersham plc	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: [^{123}I]FP-CIT Injection		
Name of Active Substance: [^{123}I]-Ioflupane		

Test Product, dose, mode of administration, and batch:
[^{123}I]FP-CIT was administered as a single intravenous injection containing approximately 111MBq in a maximum volume of 1.5 mL. Multiple batches of [^{123}I]FP-CIT were issued for use during this study. A listing of batch number used per subject is provided in Appendix 15.1.6.

Duration of treatment:
One day duration.

Reference therapy, dose, batch number and mode of administration:
None

Criteria for evaluation:
SPECT imaging was performed using a Strichman Medical Equipment 810X consisting of 12 individual crystals, each equipped with a focusing collimator. Each subject was imaged at 6 time-points post [^{123}I]FP-CIT injection. The first scan was acquired at 10 minutes post injection and represented a static scan, the remaining five scans were acquired at 1, 2, 3, 4.5 and 6 hours post injection and represented dynamic SPECT scans.

Routine laboratory assessments including haematology, biochemistry and urinalysis were conducted at baseline screening, 1 hour prior to [^{123}I]FP-CIT injection, and at 6 hours and 24-72 hours post-injection. All laboratory analyses were conducted and reported by the local laboratory at the Academic Medical Centre, Amsterdam. Each laboratory parameter was reported in reference to normal values provided by the laboratory.

Vital signs (blood pressure and heart rate), and temperature were assessed at baseline screening, 1 hour prior to injection, and 3 hours and 24-72 hours post-injection using standard methods.

Standard 12 lead electrocardiogram (ECG) recordings were performed for all subjects over a 20 minute period 1 hour prior to [^{123}I]FP-CIT injection, and at 3.5 hours post [^{123}I]FP-CIT injection.

Adverse events were assessed throughout the study.

Name of Company::	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Nycomed Amersham plc		
Name of Finished Product:	Volume:	
[^{123}I]FP-CIT Injection		
Name of Active Substance:	Page:	
[^{123}I]-Ioflupane		

Statistical Methods:
Individual data for each brain area obtained by imaging were corrected for radioactive decay and averaged. Possible time trends in ratios of uptake in brain regions were determined by repeated non-parametric analysis of variance (ANOVA). Differences in groups were analysed with the Wilcoxon's two-sample rank sum test. In the case of multiple comparisons the Bonferroni correction method was used. In all statistical analyses, probability values of <0.05 were considered significant.

There was no formal analysis of safety data planned or conducted for this study. Relevant datasets were summarised, tabulated and graphed.

Summary Conclusions:
This study shows that [^{123}I]FP-CIT is taken up rapidly into the striatum and that the ratio of specific to non-specific striatal binding was stable and significantly different between patients with Parkinson's disease and healthy controls between 3 and 6 hours post-injection. It concludes that between 3 and 6 hours post [^{123}I]FP-CIT injection would provide a suitable time window for diagnostic imaging.

In a sub-set of five hemi-Parkinson's patients even the ipsilateral striatal binding ratio was significantly different to controls, suggesting that [^{123}I]FP-CIT is potentially capable of detecting early Parkinson's disease. Estimates based on striatal uptake of [^{123}I]FP-CIT suggest a maximum transporter occupancy of 1%, a level at which no pharmacologic effect would be anticipated.

The results from this study have confirmed that [^{123}I]FP-CIT is a pharmacologically safe radioligand suitable for administration to healthy volunteers and patients with dopaminergic deficits. There were no clinically significant laboratory findings observed throughout the duration of the study. Similarly no clinically significant abnormal vital signs, temperature or ECG data was obtained.

Date of Report:
3rd September, 1998

5.0 ETHICS

5.1 Independent Ethics Committee (IEC)

The protocol (dated October 26th, 1996), and appendices for study 094/96/2370 were submitted by the principal investigator to the local independent ethics committee for review. Written approval/favourable opinion from the local IEC was provided on December 10th, 1996. Subjects were not recruited into the study prior to the receipt of the written approval/favourable opinion.

One protocol amendment (094/96/3642, dated November 26th, 1996) was issued. This amendment was prepared at the request of the local IEC, and was submitted for review. Written approval/favourable opinion for the amendment was provided in conjunction with the protocol on December 10th, 1996.

The approval letter for the study protocol (094/96/2370) and the protocol amendment (094/96/3542) are provided together with a list of local IEC members in Appendix 15.1.3.

A copy of the final protocol and protocol amendment are provided in Appendix 15.1.1.

5.2 Ethical Conduct of the Study

This study was conducted in a manner consistent with the ethics encompassed within the "Declaration of Helsinki" and in accordance with European GCP and Farma Research standard operating procedures (SOP's).

All written documentation resulting from interaction with the local IEC in relation to this study have been archived as essential documents by the investigator, the Sponsor company and the contract research organisation (CRO) Farma Research.

5.3 Subject Information and Consent

The principal investigator and/or his appointed delegate was responsible for ensuring that all subjects (Parkinson's disease patients and healthy volunteers) were adequately informed about the study both verbally and in writing. The contents of the information sheet and informed consent, provided in the local language for both patients and volunteers, were agreed between the Sponsor, the principal investigator and the local IEC prior to issue to subjects, and included the basic elements of Informed Consent as outlined in the "Declaration of Helsinki" and European GCP.

EUROPEAN COMMISSION

SECRETARIAT-GENERAL

01 -08- 2000

Brussels,

SG(2000) D/ 105731

BY COURIER SERVICE

Nycomed Amersham plc
Little Chalfont
Buckinghamshire HP7 9NA
United Kingdom

Subject: NOTIFICATION PURSUANT TO ARTICLE 254 OF THE EC TREATY

The enclosed Decision is transmitted to the Member States.

For the Secretary-General

Paul LAFILI

Encl. C(2000) 2331

Rue de la Loi 200, B-1049 Bruxelles/Wetstraat 200, B-1049 Brussel - Belgium - Office: Brey 13/24
Telephone: direct line 32 (0) 2 295.23.64, exchange 32 (0) 2 299.11.11. Fax: 32 (0) 2 295.01.20
Telex: COMEU B 21877. Telegraphic address: COMEUR Brussels.

COMMISSION OF THE EUROPEAN COMMUNITIES

Brussels, 27 -07- 2000
C(2000) 2331 - EN

COMMISSION DECISION

of 27 -07- 2000

granting the marketing authorization for the medicinal product for human use,

"DaTSCAN – ioflupane (^{123}I)"

(Only the English text is authentic)

(Text with EEA relevance)

COMMISSION DECISION

of 27 -07- 2000

granting the marketing authorization for the medicinal

product for human use,

"DaTSCAN – ioflupane (^{123}I)"

(Only the English text is authentic)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products[1], and in particular Article 10(1) and (2) thereof,

Having regard to the application submitted by Nycomed Amersham plc, on 18 December 1998, under Article 4(1) of Regulation (EEC) No 2309/93, concerning the medicinal product, "DaTSCAN – ioflupane (^{123}I)",

Having regard to the opinion of 16 March 2000 of the European Agency for the Evaluation of Medicinal Products, formulated by the Committee for Proprietary Medicinal Products,

Whereas:

(1) The medicinal product, "DaTSCAN – ioflupane (^{123}I)", complies with the requirements of Council Directives 65/65/EEC[2], 75/318/EEC[3] and 75/319/EEC[4], as last amended by Directive 93/39/EEC[5];

(2) The measures provided for in this Decision are in accordance with the opinion of the Standing Committee on Medicinal Products for Human Use,

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[1] OJ No L 214, 24. 8. 1993, p. 1.
[2] OJ No 22, 9.2.1965, p. 369/65.
[3] OJ No L 147, 9.6.1975, p. 1.
[4] OJ No L 147, 9.6.1975, p. 13.
[5] OJ No L 214, 24.8.1993, p. 22.

HAS ADOPTED THIS DECISION:

Article 1

The marketing authorisation referred to in Article 3 of Regulation (EEC) No 2309/93 is hereby granted in respect of the medicinal product: "DaTSCAN – ioflupane (^{123}I)" whose characteristics are summarised in Annex I hereto. This medicinal product shall be entered in the Community Register of Medicinal Products under the number:

EU/1/00/135/001 DaTSCAN - Ioflupane (^{123}I) - 74 MBq/ml - Solution for injection - Intravenous use - Glass vial, 1 x 10 ml, containing 2.5 ml solution

Article 2

The marketing authorisation concerning the medicinal product referred to in Article 1 shall be subject to compliance with all the conditions, particularly those relating to manufacture and/or importation, control and issue referred to in Annex II.

Article 3

The labelling and package leaflet concerning the medicinal product referred to in Article 1 shall conform to Annex III.

Article 4

The period of validity of the authorisation issued shall be five years from the date of notification of this Decision. It shall be renewable under the conditions laid down in Article 13(1) of Regulation (EEC) No 2309/93.

Article 5

This Decision is addressed to Nycomed Amersham plc, Little Chalfont, Buckinghamshire HP7 9NA, UNITED KINGDOM.

Done at Brussels, 27 -07- 2000

For the Commission

Erkki LIIKANEN
Member of the Commission

COMMISSION OF THE EUROPEAN COMMUNITIES

CERTIFIED COPY
The Secretary General,
p.o.
David O'SULLIVAN